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Surveys of Foreign Scientific and Technical Literature

SOVIET VIROLOGY

ATD Work Assignment A-67-7

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TABLE OF CONTENTS

Inti	rodu	etior	1.		•	•	. ,	•	•	•	•	•	•	•	•	•		•	•	. iv
I.	The A. B.	Tick Epic Behs	iemi	010	gic	al	Da	ta	٠.	•		•	•	•	•	•	•	•	•	• 2
	c.	Tiss Indu	ue	Cul	tur	e			•	• • •	ra ~	•	•	•	•	•	•	•	•	• 4
		Diag	rcen	1 PIU	UA U	±b.	uya 11 O	ر <u>د</u>	אני געני	בוווי קיינ	 ≀.r.⊤	·ue	es	•	•	•	•	•	•	• 5
	E.	TRE	The	ran	v V	Ç11	ous	Τ,	J 1	11	ندر	•	•	•	•	•	•	•	٠	• 0
		1.	Vac	cin	es	•			•	•	•	•		•			•	•		• 9
		2. Japa Omsk	Cha	lle	nge	:	• •	•	•	•	•	•	•	•	•	¢	•	•	•	• 9
	F.	Japa	mes	e B	En	ce	pha	111	118	3	•	•	•	•	•	•	•	•	•	. 13
	G.	Omsk	c P	rer	an	d	Rel	ate	e₫	Di	.86	as	es	١.	•	•	•	•	•	.13
H.	Нос	of-ar	ıd-M	out	h D	ris	eas	е	•	•	•	•	•	•	•	•	•	•	•	. 25
IH.	. Ra	abies	3 .	• •	•	•		•	•	•	•	•	•	•	•	•	•	•	•	. 26
IV.	Syr:	ine F	'lag	ue	•	•		•	•	•	•	•	•	•	•	•	•	•	•	• 32
v.	Ven	ezuel	.an	Equ	ine	E	nce	pha	aic	Anz	re]	Lit	is	3 1	•	•	•	•	•	• 33
VI.	M1:	scell	.ane	ous	Di	.se	ase	8	•	•	•	•	•	•	•	•	•	•	•	• 34
VII.	. P	tV-xc	lrus	In	fec	ti	ons	•	•	•	•	•	•	•	•	•	•	•	•	•37
Refe	eren	ces	•		•	•		•	•	•	•	•	•	•	•	•	•	•	•	.40
Appe	end1:	x I.	Su	ppl	eme	nt	ary	B	lb]	lic	gı	rap	h	7	•	•	•	•	•	•70
Appe	end1:	x II.	, C	onf	ere	nc	ев	on	٧ź	Lra	11	Di	.56	88	se	•	•	•	•	.82
Appe	endi: Ins	x III titut	[. tes	Som	e S Th	ov e1	iet r P	V: er:	iro	olo	gi el	l.ce	ıl •	Re	86	ear	ecì	1	•	.91

SOVIET VIROLOGY 1962---1965
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INTRODUCTION

This report reviews literature on Soviet virological research published between 1962 and 1965, inclusive, pertaining to the development and administration of vaccines and other therapeutic preparations designed to protect humans and animals against virus diseases. It includes data on preparation and innoculation techniques and challenge tests on laboratory animals to test the effectiveness of new vaccines. Coverage of related studies in the epidemiology, detection, diagnosis, vectors, and infection cycles of viral diseases is also included. Appendices provide additional information on virus research personnel and institutions, and on virological conferences held during those years.

I. THE TICKBORNE EMCEPHALITIS COMPLEX

Viruses of the tickborne encephalitis complex are group B arboviruses and are closely related antigenically, often behaving like distinct strains of a single viral species. The Far-Eastern form of the disease is usually more virulent than the European form [275]. Tickborne encephalitis (TBE, RSSE, Far-Eastern encephalitis, biphasic (two-wave) meningo-encephalitis, etc.) has a broad host range but is usually spread by ixodid or closely related ticks, generally Ixodes persulcatus and Ixodes ricinus.

Fleas have been implicated as vectors as well [244, 281, 111, 282]. In one study, the species composition, host range, and population dynamics of fleas in the Kalinin, Perm, and Kemerovo oblasts were studied. It was found that fleas transmitted the virus to rodents within 6 hours after their birth; this explained the relatively high antibody titers in the rodents and the low numbers of ixodid tick larvae and nymphs found in the vicinity of burrows. Transmission by fleas was confirmed experimentally [110].

Virological studies of ticks in epidemic regions are made regularly, especially during peak infective periods [110, 109, 261, 41, 233].

Hundreds of distinct strains have been isolated, including several strains that are antigenically and morphologically different from standard strains and are often highly pathogenic in tissue cultures [109, 41]. Birds, rabbits, livestock, hedgehogs, and other wild animals are also TBE vectors [164, 55]. TBE virus has been isolated from thrushes (Oriocichia dauma) carrying Ixodes persulcatus ticks [275, 248] and from hedgehogs, which maintain the virus during hibernation after being infected by tick bites or by eating contaminated food [143, 255, 74, 264].

A large-scale survey of virological and serological data on arboviruses isolated in the eastern Soviet Union revealed TBE, EEE, WEE, and Chikungunya virus in over 1000 samples from epidemic foci in Siberia, the Irkutsk region, eastern Kazakhstan, and other regions [59, 26]. Secondary examination of insect, bird, animal, and human organs and tissues from eastern

Kazakhstan yielded data on the first isolation of Casals group A viruses in the eastern USSR [12,91]. Strains K-10, K-13, and K-16 isolated from mosquitoes produced symptoms within 24 hours. Strains PT-149, PT-151, PT-161 and PT-182 isolated from the birds Sturnus vulgaris, Corvus corona, and Larus ridibundus had incubation periods lasting from 1--8 days [12]. Transovarian transmission of TBE virus has been demonstrated in a small rercentage of certain tick species. Its potential importance is that it ensures the infection of a large number of larvae and consequently, wide discemination amoung the local smallmammal population. The species displaying this trait are Ixodes persulcatus, I. rincinus, I. hexagonis, Dermacenter silvarum, Haemaphysalis concinna, and H. japonica. Experimental infection of I. ricinus showed that artificial means of infection could be used. Among females, 3.3% transmitted the virus when they were infected by feeding on infected mice and 21 % when the virus was injected directly into the body cavity. Although the latter method produced better results, the inoculation process was often fatal to the ticks. The strains did not lose their cytopathogenicity during transovarian passage [249].

A. Epidemiological Data On the Tickborne Encephalitis Complex

At a conference on arbovirus infections held in Moscow in September 1964, the Eleventh Scientific Session of the Institute of Policryelitis and Virus-Encephalitis Discases of the Academy of Medical Schences was devoted to discussion of tickborne encephalitis, Omsk fever, Kemerovo tick fever, and related diseases [203]. During the four days of the session, 85 papers were presented which were later incorporated into the published collected papers of the meeting. All aspects of these diseases from classification of the viruses to prophylaxis and immunization were discussed. A paper presented by A. M. Butenko and Ye. S. Sarmanova on the isolation of new virus strains in Kemerovo and Astrakhan oblasts complements the work of M. P. Chumakov et al. on the isolation of a serologically distinct member of the TBE complex which was accomplished during the joint Czech-Soviet virological expedition during the summer of 1952. This expedition made virological examinations of ixodid ticks, suspected human carriers, and healthy persons bitten by ticks in Western Siberia. Both typical and atypical strains were isolated. In one

region, 20 serologically similar strains were discovered which produced a febrile type of encephalitis in humans. The new virus strains were cytopathic in chick tissue culture in 48--72 hours, multiplied well in the yolk sacs of 7-day chick embryos, were fatal to newborn white mice but generally not to adults, and were antigenically distinct from the rest of the encephalitis complex although they produced similar symptoms. Later, 20 similar strains were isolated which were remarkably pathogenic to intracerebrally inoculated rats and hamsters, producing brief fever in Rhesus monkeys and having varied effects on tissue cultures [40]. A report of a test of a new cultural inactivated vaccine made on a million subjects was given by D. K. L'vov, and data on its production technology and quality control were given by A. V. Gagarina and I. M. Rodin. Kemerovo tick fever was discussed at a special Immunological shifts in humans, the capacity of the virus to agglutinate erythrocytes, morphology, and the isolation of similar viruses in other parts of the Soviet Union were also considered [203].

In typical epidemic foci, sizable percentages of captured ticks carried highly active virus [182, 232]. In some foci the outbreaks have a mosaic pattern which, some Soviet scientists suggest, depends on the variable virulence of the local strains isolated during epidemics [186]. A high percentage of wild and domestic animals and wild birds usually carry viruses, and humans in such districts usually have complement - fixing antibodies in high titers [155]. At least one case of a patient with relapsing TEE has been reported [123]. Simultaneous cases of both TBE and Omsk fever have been reported in humans and both diseases usually increases in occurrence with increases in the rodent and ectoparasite population, pointing to similarities in their mode of distribution since they are antigenically distinct [263, 59].

A study on comparative natural immunity in reptiles susceptible to TBE virus showed that in reptiles infected with TBE by various routes under different temperature conditions and by different techniques, temperature was found to be the most important single factor changing immune response. No immune response was observed in Eremias velox and Agama caucasia individuals kept at 4°C, whereas the earliest appearance of antibodies and the highest antibody titers occurred in individuals kept at 37°C [273].

B. The Behavior of TBE Virus in Cell and Tissue Culture

Czech researchers have found that in tissue cultures inoculated with two or more viruses. cell resistance involves formation of interferon-like inhibitors that suppress the invading virus in cultures already adapted to one type of virus [9, 227, 207]. This phenomenon is the tasis for a method in which TBE virus can be titrated by determining cytopathic effect in tissues infected with polioviruses. In this method, the TBE viruses resisted he effects of poliovirus, and by some mechanism not yet known, but probably involving production of an interferontke sustance, inhibited the cytopathic effects of poliovirus [8]. Such an interference method can be used to aluate the effectiveness of TBE vaccines. A method reported in 1963 by Al'shteyn et al. was economical and precise, but was more time-consuming than intracerebral inoculation of mice [11]. A plaque-assay method, on the other hand, depends on the definitive identification of plaques; any condition that interferes with plaque formation is to be avoided. Cells, therefore, must not be pretreated with interferon if plaques are to be clear. This method can also be used to obtain viral clones by repeated plaque isolation and subculturing in newborn mouse brain [100].

Many cell and organ cultures have been screened as suitable media for the evaluation of inocula and vaccines. Comparative evaluation of tissue lines by Karaseva and Semenov confirmed the suitability of chick-fibroblast or swine-embryo tissue [13, 14, 15, 92]. Titration in human-embryo fibroblasts has yielded results 50 times less sensitive than the intracerebral inoculation of mice, but within its effective range it is clearer, more precise, and reproducible, and can be used for detecting neutralizing antibody [10, 56]. Tick tissue culture is reported as the best medium for the early detection of tickborne encephalitis virus since a marked cytopathic effect is produced by small quantities of virus [189]. In growing virus in tissue cultures, agitation was shown to aid in the production of higher titer [75, 137]. Chick-embryo tissue was best for work in which gradual and continual release of virus from cells without marked cytopathic effect was desired [154]. Several authors report a "partial" cytopathic effect in lines that have been chronically infected with the virus, with a reduction in virus multiplication rate and a consistently low percentage of cellassociated virus (usually 1 % intranuclear) with the rest in the culture fluid [138, 16, 19]. Some cell lines are

affected by medium composition with consequent changes in cytopathic effect [139], and all cultures of mammalian cells also had a resistance to superinfection as discussed above, although long-term culturing could not eliminate persistent infections [141].

5

The effects of long-term culturing on TBE viruses has been studied at the Moscow Scientific Research Institute of Viral Preparations. Culture conditions played an important role in the properties of some mutant strains, and others maintained their properties unchanged even under prolonged culturing and varying temperatures. strains developed the ability to destroy SMH and chick fibroblasts after adaptation [17]. The laboratory of V. V. Pogodina of the Institute of Poliomyelitis in Moscow has investigated the variable pathogenicity (virulence) of TBE and related strains for different laboratory animals under varying conditions. Various strains of TBE, Langat, Omsk fever, Louping ill, Powassan, and Kyasanur forest fever viruses were studied for both intracerebral and peripheral pathogenicity in attempts to use neurovirulence as a strain marker. They observed the following types of neurovirulence: a) high intracerebral and high peripheral--Eastern and Western TBE strains, and Omsk fever, Kyasanur, and Powassan viruses; b) low intracerebral and high peripheral -- Khab-9 and Vasenkova strains (EEE); c) high intracerebral and low peripheral -- Fatayev and Ix-2 (TBE); and d) low introcerebral and low peripheral--Langat strain TR-21, recommended as a vaccinal strain. Mice and hemsters were judged unsuitable for differential diagnosis of the TBE complex since they displayed uniform clinical symptoms with all strains. Lambs were ruled unsuitable because of their low susceptibility. While none of the animals tested were equally susceptible to all the strains, newborn pigs were the most suitable for differentiating strains on the basis of virulence [178, 177].

When a newly isolated TBE strain was injected into young mice and passaged, its virulence decreased. Specific resistance to challenge by the original wild-type virus was produced by injection with this attenuated strain; degree of immunity was affected by virus dose and time of immunization. The lowered virulence was connected with a decrease in the ability of the attenuated virus to multiply in extraneural tissue [107, 143, 179]. Since titration on the basis of cytepathic effect gave inconclusive results [180], the flucrescent-antibody method (FAM) was

employed in the tissue-culture studies of growth stages, of the appearance of viral antigen, and of cytopathic effects of Langat (strain TR-21) virus, a weakly virulent virus demonstrating antigen visually.

C. Induced Mutation of TBE Viruses

G. D. Zasukh na and I. A. Rapoport reported on the chemical mutagenesis of TBE viruses. General studies of the variance in hered: ary characters resulting from treatment with various chemical mutagens produced mutant strains of varying virulence and morphology [286]. Changes in cytopathic effect in tissue culture were not connected with cytopathic effect in cell cultures treated with 5-bromouracil, formaldehyde, urethane, and a combined proflavin-urethane preparation [285]. In the work of Zasukhina and Rapoport, the effects of some standard mutagens on two groups of arboviruses with characteristically low and high mutation rates are compared. Strains of TBE virus with a characteristically low mutation rate and WEE strains with a higher mutation rate, better culturing properties, and a faster growth rate were treated with: 1) 5-bromouracil, 2) formaldehyde, 3) l,4-bisdiazoacetylbutane and 4) N-nitrosomethylurea. These mutagens produced alkylation of the hereditary material; 1, 2, and 4 yielded a greater percentage of apathogenic mutants than did 3. A greater number and variety of mutations were produced by 1,4-bisdiazoacetylbutane. These results were highly significant in explaning "zoclogical cosmopolitanism, ability of these viruses to survive in dozens of species of cold and warmblooded animals. These animals are the reservoirs, carriers, and victims of these viruses. A secondary aspect of the study was to determine the range of artificially induced mutant properties of these viruses with the intention of creating live vaccine strains from strains with induced mutation. Several strains were selected for further study [287].

D. Diagnostic Methods for Tickborne Encephalitis

The fluorescent-antibody method

The principal advantages of the fluorescent-antibody method (FAM) in diagnostics are speed, accuracy, and the saving in reagents [128, 145, 156]. This method has been employed to detect cell-bound and free TBE viral antigens in sheep-kidney cultures [129], and shows the intracellular distribution of nucleic acids and specific antigen in mouse-brain and sheep-embryo kidney tissue [220, 219]. This method has been used diagnostically and in the study of the course of experimental infections. It is easily and rapidly detectable in the central nervous system and lymph nodes scon after infection, usually within 24 hours. Viral antigens are easily demonstrable even in animals showing no clinical symptoms [83, 146].

Complement fixation reactions

<u>-3.</u>

Complement fixation is repeatedly cited as one of the best methods for diagnosing TBE (though the FAM is superior) [64, 54, 150, 39]. Its principal disadvantages, the length of time required to obtain definitive results (as much as 15--30 days) [64, 103] and the relatively sophisticated equipment required, make hemagglutination more acceptable [63]. A method by which dried blood on filter-paper disks is used was ruled unsuitable for the complement fixation reaction because of the large titers of anticomplementary substances in the dried blood [54]. However, this system is adaptable to the neutralization reaction [54], although in most papers on neutralization, it is carried out in vitro or in tissue culture [255]. The principal advantages of either fast neutralization or complement fixation is the elimination of mice. Also, since the virus multiplies faster in tissue culture than in mice, virus can be obtained, identified, and typed more rapidly [64]. Several papers report the processes of obtaining and purifying sera for complement fixation [150, 266, 58, 38].

Hemagglutination and hemagglutination-inhibition reactions

Hemagglutination and hemagglutination inhibition have been used diagnostically in large-scale serological surveys and epidemiological studies both in the field and in tissue cultures [276, 95, 126, 200, 171]. Sheep-embryo kidney cultures provide the most suitable medium for hemagglutination and for complement fixation, although use of other tissues is reported in the literature [62, 96, 223, 47, 53]. TBE hemagglutinating antigens obtained from viruses grown in various tissue cultures are highly specific, require no elaborate purification process, and are stable at 4°C. They were therefore recommended to

replace brain-derived antigens for serodiagnosis of TBE. The accumulation of virus in the culture media can be determined fairly accurately by hemagglutination and TBE virus can be detected in experimental mixed infections in tissue culture [150]. A modified hemagglutination-inhibition (HI) reaction is widely used in the Soviet Union in surveys of known and suspected vectors [201, 171, 275, 97]. One method, which enables a technician to determine the presence of TBE and Japanese encephalitis antigen without the complement-fixation reaction, involves the simultaneous performance of the HI test over a wide pH range, since the Japanese and TBE viruses agglutinate at different pH values [247]. A further modification of this test suitable for large-scale work employs paper discs and requires minute blood samples [201]. Since antigens are plentiful in the blood long before the appearance of clinical symptoms, Gaydamovich and others have recommended the HI reaction for early detection of arboviruses and suggest its use in the identification of vectors [67]. Use of this reaction to demonstrate the presence of TBE antigen in wild birds and their parasites is particularly interesting as it enables contacts of wild birds with epidemic foci to be revealed [171].

A modified precipitation reaction was chiefly used in typing and determining antigenic relationships rather than in diagnosis [224].

Neutralization

The chief benefits of neutralization methods have been found to be that clear-cut results could be obtained within 72 hours with freshly isolated strains and with convalescent sera; even sera contaminated by bacteria could be used and the tests could be carried out in ordinary culture bottles without impairing sensitivity [255, 131, 52]. Disadvantages were such external factors as season [274]; also, clinical manifestations in a given individual affected the neutralization indices so that a definite hemagglutinin-forming dose could not be determined accurately [255, 20]. This method could be used to detect infectious RNA in the course of an investigation of the properties and functions of TBE virus RNA [49].

A colorimetric test for TBE has been used experimentally with success; its only disadvantage is that definite results may be obtained only after 4--5 days. Further research on this test is underway [93].

Plaque formation has been used in the differential diagnosis of TBE because its plaques are distinct from those formed by other viruses. In one experiment, TBE virus formed large turbid plaques, Omsk fever virus formed small plaques, and Langat virus (strain TR-21) formed both large and small transparent plaques, indicating the heterogeneous composition of the inoculating strain [122]. Standardization of conditions is very important since agar inhibitors also alter plaque sizes [51]. Positive identification may be made in 3--4 days using a method reported by Logina-Parina in 1964 [121]. The infectivity of TBE infective RNA can also be shown by the plaque technique [50].

E. TBE Therapy

4.5

1. Vaccines

A 5% brain vaccine against TBE was administered to mice and guinea pigs. This vaccine was prepared from serum obtained from infected animals two or four days after infection, and was administered in two doses 28--32 days apart. When an allergic reaction appeared, the animals received normal brain suspensions or formol-inactivated vaccine as desensitizers. In guinea pigs, tissue from sick mice and from infected mice which had not yet displayed clinical symptoms produced strong anaphylactic reactions. Four-day vaccine caused only a weak response, leading to the conclusion that intermediate antigens appeared between the second and fourth day after injection [13].

A nonallergenic, formolized vaccine was obtained by Gagarina et al. by the intracerebral infection of newborn rats. Similar vaccines have been obtained by others [60, 83, 115, 260]. Vaccines adsorbed on aluminum hydroxide possessed greater immunogenicity than native vaccines [115].

Vaccines prepared from tissue cultures were generally more effective and easier to handle and store, and were areactogenic as compared to inactivated brain vaccines. In general, greater postinfection immunity was observed with the tissue-culture vaccines [43, 202, 258]. Rates of antibody accumulation and immunological shift varied during large-scale trials. High antibody titers appeared rather early [44] in some previously unvaccinated persons and after considerable delay in others, suggesting to the

researchers that threee immunizations were optimal. Large-scale trials bore this out, leaving the question of the optimum intervals to be determined [259]. The immunizations last at least six months [257, 46]. In trials with human volunteers, Chumakov and his associates found that maximum immunogenicity was obtained when shots were given 1-4 days apart followed by a booster after six months, especially in tests of nonadsorbed vaccines [46].

Attenuated vaccines prepared in tissue cultures were more effective than brain vaccines in almost every case, though their effectiveness was affected by such external factors as drugs and hormones [42, 199]. It has been established that the regional lymph system limits the penetration of tickborne encephalitis virus into the bloodstream under experimental conditions [132]. Cortisone treatment of mice at the time of immunization did not improve the prophylactic effect of the vaccines; on the contrary, viremia lasted longer in animals receiving cortisone [98, 253]. X-irradiation speeded the spread of TBE virus through the regional lymphatic system except in the lungs, where a decrease in virus titers was noted [130]. Urethane-barbital preparation had much the same effect as cortisone on experimental TBE infections in mice, with viruses persisting longer and in higher titers [199]. tissue culture vaccine effective against both eastern and western forms of the TBE complex and possibly against related diseases and which possesses almost the same virus-neutralizing capacity for all the diseases of the TBE complex was developed at the Institute of Poliomyelitis in Moscow by Zaklinskaya and coworkers [283].

Antisera and specific globulins have been found the most suitable for use in epidemic foci because of their areactogenicity and because they are easily obtainable [57, 182]. A-type immune serum against tickborne encephalitis is specific, shows no anticomplementary activity, and contains no antibodies to brain tissue; it can be used as a standard in complement-fixation and hemagglutination-inhibition tests with TBE antigen [194].

STORAGE PROPERTIES OF THE VACCINES

Of the wet vaccines, formol-inactivated vaccines were the most stable, with a shelf life of up to 9 months. Some batches were kept in rubber-stoppered common glass bottles up to one year [35, 83, 198]. Dried vaccines kept longest, provided residual moisture did not exceed 1% [125].

Studies of the properties of viral infection in tissue culture have been made in the laboratory of J. Vilcek in Czechoslovakia. Several reports on the formation, antiviral action, and comparative properties of various interferons have been published. When mice are infected with TBE intraperitoneally or intracerebrally, high interferon levels are found in the brain of inoculated animals [269]. When cells infected with WEE, EEE, vaccinia, NDV, and homologous TBE viruses were treated with interferon from TBE-infected cells, their resistance to the other diseases increased [267]. The action of TBE-interferon and influenza-interferon was compared; results were found to be similar to those of the previous study, indicating that the specific inducing virus fails to influence the properties of the interferon formed in a given cell culture [70, 185, 268].

The following enemicals and other preparations have been more or less successfully tried as decontaminants and therapeutic compounds for virus alseases in the Soviet Union: Lactams and Lactones, especially beta-propiolactone, were recommended for general disinfection use and for further study [173, 293]. Novembichin and other antibiotics were somewhat effective [28, 73]. Dichloroethylamines showed antiphage action and ethyleneimines inhibited the action of many viruses [27, 29, 288]. Naturally occurring, interferon-like inhibitors in both live animals and in tissue cultures have been reported in many papers. Most of them are enzymatic and thermolabile [147, 217, 228, 246, 250, 292].

Uniformly satisfactory results have been obtained with the administration of vaccines, drugs and therapeutic chemicals by means of aerosols [4, 5, 6, 7, 66, 77, 183. 187, 270, 271, 289, 290]. In fact, some live, attenuated vaccines are most effective when administered by aerosol in very small quantities [66].

A killed tissue vaccine prepared from TBE virus strains Yas-8 and Ix-10 was tested on animals kept in a IVK-2 chamber. Vaccinations were given at 1-, 3-, 5-, 7- and 10-day intervals via an aerosol with particles averaging 1--3 microns in diameter. This method produced a rapid rise in virus-neutralizing antibody titer and successfully protected animals challenged with the virus. The vaccine penetrated the tissue rapidly, enabling smaller doses to be used. A mixed aerosol conferred immunity to both viruses (TBE and WEE) [250].

2. Challenge of Animals Vaccinated Against Tickborne Encephalitis

There are numerous reports of challenge tests of vaccinated animals to determine the efficacy of certain methods of immunization and the properties of experimental vaccines. In a study to determine the conditions influencing the effectiveness of TBE prophylaxis in human volunteers and the relationship of the immunogenic properties of the vaccine and its immunologic effect, 548 persons, all previously unvaccinated, received doses of vaccine at 1-2 and 2-3 week intervals. They were revaccinated after 1 year. Twelve types of tissue culture vaccine and three types of brain vaccine were tested. Conclusions reached were that if the first series of shots possessed highly immunogenic properties, then a booster possessing diminished immunogenicity was effective. The reverse was not true [45].

Some of the standard vaccines, particularly the mouse-brain vaccine, are easily contaminated by bacteria and produce allergic reactions. Thus, tissue-culture monolayers, especially chick-embryo cultures, are considered a superior source for vaccines. Formalin or beta-propiolactone were used as neutralizers to make the vaccine suitable for use. Optimum inactivation conditions were determined. A satisfactory vaccine was prepared by inactivation at 4°C. (This was necessary because the 37°C temperature of some methods destroyed the immunogenicity of the virus). vaccine had a shelf life of approximately 6 months and protected challenged mice against high concentrations of In tests on humans with low or nonexistent serumantibody titers, 66% of volunteers developed antibodies in sufficiently immunizing titers within 4 weeks after vaccination [84, 127].

Airborne infection of monkeys with TBE virus produced little CNS involvement, but other symptoms produced were like those evoked by infection from other routes [23, 114]. In two studies the infective dose for aerosol infection was found to be 10^4--10^5 i.c. mouse LD50. In both cases, active immunization with TBE vaccine was the best way to protect test animals against high infectious titers [23, 48]. Airborne infection is an unusual route and occurs mainly, or perhaps entirely, in the laboratory. In these studies animals were kept in a special flow chamber and aerosols were generated by a specially developed appara-

tus which generated particles with average diameters of 0.75-1.5 microns. The dose could be varied by altering the concentration of virus in the carrier fluid or by varying exposure time. A Formol vaccine offered animals better protection against aerogenic infection than against infection by other routes [48].

F. Japanese B Encephalitis

Virological surveys have shown birds to be an important factor in the dissemination of Japanese B virus. A survey of the southern Primor'ye showed the presence of hemagglutinating and complement-fixing antibodies in 200 wild birds of 36 species [166, 181]. Sheep-embryo kidney tissue culture is the most widely used medium for the evaluation of cytopathic effect in the diagnosis of the disease since no preliminary adaptation is required. The cytopathic effect is limited in adult tissue cultures [61, 165]. attempts to culture the virus in guinea-pig tissue involve the nece sity of intracranial infection of the initial animal with a suspension of infected chick tissue, and intractanial subculturing. This laborious procedure yields a preparation with unchanged antigenic properties after long passaging [197]. Noninfectious diagnostic sera and hemagglutining for the HI test have been produced [68, 237]. Uvarov and his associates prepare concentrated hemagglutinins by precipitation in ammonium sulfate and incubation at pH 3.2--8.5 for 19--24 hr at 0--4°C [264].

G. Omsk Fever and Related Diseases

Omsk fever and other renal hemorrhagic fevers present diagnostic problems similar to those surrounding the identification of various forms of the tickborne encephalitis complex. In addition, Omsk fever and Kyasanur forest disease are antigenically related to tickborne encephalitis. Hemorrhagic nephroso-nephritis (HNN) and Omsk fever are often misdiagnosed as leptospirosis, tickborne encephalitis, gastroenteritis and other diseases. The tables compare the characteristics of HNN and related diseases and abdominal conditions for which it is most often mistaken.

Table I from [216]

COMPARATIVE CI: SICAL CHARACTERISTICS OF HEMORRHAGIC FEVERS

COMPARATI	AL CI. MCM. CHERACIE	RISTICS CY TENCRIOTACI	C PEPERS
Hemorrhagie nephrotie - nephritis	Crimean hemorrhagic fever	Central Asian herror- rhagic fever	Omsk hemorrhagic fes cr
	Predominant clini	cal syndrome	
Distinct hemorrhagic manifestations and a severe general intoxication at the height of the disease, acute renal damage and utimary exerction impairment, tometimes acute renal failure.	Phenomens of general intakes to m with distinct to m with distinct to morthagic phenomena and relatively mild neurological lesions.	Very severe general in- toxication and distinct severe damage to the gastrointestinal tract, with massive, frequent- ly critical bleeding	Relatively mild general intoxication and hemor- thagic diathesis. Dis- tinct respiratory tract lesions.
	Incubatio	a period	
From 11 to 23 days. On the average 14-15 days.	From 2 to 25 days.	3~4 days. Especially short in intramural hospital infections.	2-4 days. Especially short in infections of personnel caring for infected laboratory animals.
	Frodrom	al period	
Observed rarely. Lasting 2-3 days.	Prodremal period not manifested.	Prodromal period not manifested,	Rarely observed.
Cyc	les of development of the o	linical picture of the diseas	é
Four periods of the disease: the first general febrile period.	Three periods of the dis- ease: the first initial period.	Three periods of the dis- ease: the first initial period.	Two periods of the disc w the first, febrile period
Second period - herror- magic manufestations, Third period of maximal injuries to organs, Fourth period - re- convalescence.	Second period - height of the disease. Third period - re- convalescence.	Second period - Feight of the disease Third period - re-convalescence.	Second period — apyresia, reconvalescence.
Temperature often rises suddenly to 39-40°C and remains high until the 4th-7th day of the disease, later resolving by lysis in 2-3 days	Temperature rises suddenly to 39-40°C and then resolves by lysis after 7-8 days. A characteristic brief drop in temperature on the 3rd and 4th days of the disease coinciding with the beginning of the hemorrhagic manifestations.	After a severe chill the temperature rises suddenly to 39-40°C and drops somewhat on the 3rd or 4th day (with the beginning of hemormagic manifestations). Later it remains at a level of 37-38°C to the 7th-8th day of the lisease and later returns to normal by lysis.	After a brief chill temperature rises suddenly to 39-40°C. It resolves by lysis between the Arand 15th day of the dispease. A brief decrease on the 3rd or 4th day (beginning of hemore thagic may ifest tiens) as characteristic. In 5° of cases in the second middle week of the reduction of the secondary for the secondar

Table I continued

	Hemouhigh rephretic-	Crimean termorrhagic	Central Minsbemer-	Omsk hemormagic
	e-philite	leves	rhugic feser	leves
Color of skin	1 '' ''	Typical hyperemia of	Hyperemia of the	Hyperemia of the skin
	the skin of the face,	the skin of the face,	face not distinct,	of the face and the
	neck at dupper half	acck and upperhalf		epper half of the body
	of the body from the	of the body from the		observed in SO % of
	first hours of the	first hours of the		cases from the first
	disease and until	disease and to the		hours of the disease
	the reconsilercest	reconvalercent		and wet il the re-
	period.	period		convilescent period.
Color of	Typical hyperemia	Typical hypomesia	Hyperemia of the	Hyperenia and injection
wisible	and injection of the	and injection of	stiere, soid	כל לאר דייציא כל לאר
MUCOUS	vesels of the sole-	vessels of the	the pharma or	scierae, phagea and
membranes	tae, conjunctiva and	science, consumer	tomis was tarely	oral cavity during the
	oral cavity from the	tive and oral cavity	cherred	febelle period.
	first hours of the dis-	in the initial period		
	ease and until the	and during the	į	•
	recorralencest pe-	Pelitic of the cite.		
	nod	, -		
		£25€,	<u> </u>	
Palse	Moderate bradycardia	Moderate bradycardia	ಗಿತೀ ಚ≺ ಯಾಡ-	Moderate base, cardia
	during the first three	during the period of	ನಿರಾಧವೇ ಬಿ. ಇಬಾ.	is the febrile period.
	pedods of the dis-	Eigh temperatuse.	pentate, in	Sometimes tech;-
	ease. Relative		severe disease	Carda.
	tachycardia from	Į	counce with max-	Į
	the beginning of the		sive blood loss	
	reconsideress per		there is tacky-	
	ಗುರ	•	CAPEL.	
Bisod	Most frequently	Typical moderate	Typical distinct	Typical distinct aterial
propert	moderate hypoten-	hypotension -	hypotension, -	hypotension
••	sico -	90-100/50-50.	\$0-90/40-50.	\$0-90'40-50 during
	1	1	Depret of hypo-	the entire feballe
	\$0-100/50-50:	1		
	\$0-100/50-60;			period.
	severe hypotession		tention derectly	period
	(collapse) or hyper-		tenion dereth proportional to	period
	severe hypotession		tention derectly	period
	severe hypotention (collapse) or hyper- tension are rare.		temion derectly proportional to the degree of loss of blood.	
Hemerhagic	severe hypotection (collapse) or hyper- tension are rare.	From the 3rd-4th day	tenion dereth proportional to the degree of loss of blood. A slight petechial	A slight perechial scamy
Hemorrhagic manifesta-	severe hypotection (collapse) or hyper- tension are rare.	From the 3rd-4th day of the disease there	tenion dereth proportional to the degree of loss of blood. A slight petential rath appears to	A slight percebial scamy rath is seen only in 20%
•	severe hypotention (coilage) or hyper- tension are rare. From the Ird-4th day	1	tenion dereth proportional to the degree of loss of blood. A slight petechial	A slight percebial scarry
manifestu-	severe hypotention (coilapse) or hyper- tension are rare. From the 3rd-4th day there is a slight perceptial rash on	of the disease there	tenion dereth proportional to the degree of loss of blood. A slight petential rath appears to	A slight percebial scamy rath is seen only in 20% of patients, in the skin of the anterolateral
manifest;- tions	severe hypotention (coilapse) or hyper- tension are rare. From the 3rd-4th day there is a slight perceptial rash on	of the disease there is a small scattered petechial rash on the skin of the ar-	lenion derectip proportional to the degree of lost of blood. A slight perechial rash appeals in the first to fifth day of the disease. It is seen mainly	A slight perechial strany rath is seen only in 20% of patients, in the skin of the anterolateral surfaces of the body and
manifest;- tions	severe hypotention (coilapse) or hyper- tension are rare. From the 3rd-4th day there is a slight percential rash on the skin of the	of the disease there is a small scattered petechial rash to	tenion derectip proportional to the degree of lost of blood. A slight perechial rath appeals in the first to fifth day of the disease, it is seen mainly on the skin of the	A slight peterbial stamy tash is seen only is 20% of patients, in the skin of the anterolateral surfaces of the body and limbs. Sometimes co-
manifest;- tions	severe hypotention (collapse) or hyper- tension are rare. From the 3rd-4th day there is a slight percelular such on the skin of the lateral surfaces of	of the disease there is a small scattered petechial rash on the skin of the ar-	lenion derectip proportional to the degree of lost of blood. A slight perechial rash appeals in the first to fifth day of the disease. It is seen mainly	A slight peterbial stamy tash is seen only in 20% of patients, in the skin of the anterolateral surfaces of the body and limbs. Sometimes co-
manifest;- tions	severe hypotention (collapse) or hyper- session are rare. From the 3rd-4th day there is a slight percehial rash on the skin of the lateral surfaces of the chest, abdomen	of the Garase there is a small acamerol petechial rash on the skin of the an- terior and lateral surfaces of the cheri	tenion derectip proportional to the degree of lost of blood. A slight perechial rath appeals in the first to fifth day of the disease, it is seen mainly on the skin of the	A slight peterbial stamp rash is seen only in 20% of patients, in the skin of the amerolareral surfaces of the body and limbt. Sometimes co- alescent hemombages
manifest;- tions	severe hypotention (collapse) or hyper- sension are rare. From the Ird-4th day there is a slight perechial rash on the skin of the lateral surfaces of the chest, abdomen elbon, armpats	of the Garase there is a small acamerol petechial rash on the skin of the an- terior and lateral surfaces of the cheri	tenion dereth proportional to the degree of lost of blood. A slight perechial rish appeals in the first to fifth day of the disease, it is seen mainly on the thin of the anterior surface of	A slight peterbial stamp rash is seen only in 20% of patients, in the skin of the americanceal surfaces of the body and limbt. Sometimes co- alescent bemorrhages
manifest;- tions	severe hypotention (coilage) or hypersension are rare. From the 3rd-4th day there is a slight perechial rash on the skin of the lateral surfaces of the chest, abdomen elbow, armpair; more rarely a widely	of the Garase there is a small acamerol petechial rash on the skin of the an- terior and lateral surfaces of the cheri and abdomen. There	tenion dereth proportional to the degree of lost of blood. A slight perechial rash appeals to the first to fifth day of the disease. It is seen mainly on the skin of the anterior surface of the body and limits	A slight peterbial stamp tash is seen only in 20% of patients, in the skin of the antendateral surfaces of the body and limbt. Sometimes no- alescent bemorrhages appear in the lumbar
manifest;- tions	severe hypotention (coilage) or hypersension are rare. From the 3rd-4th day there is a slight percehial rash on the skin of the lateral surfaces of the chert, abdomen elbow, armpair; more rarely a widely distributed rash is	of the Garase there is a small scattered petechial rash to the skin of the an- terior and lateral surfaces of the cheri and abdomera. There may also be a	tenion derecth proportional to the degree of loss of blood. A slight perechial rath appears in the first to fifth day of the disease. It is seen mainly on the shin of the metric surface of the body and limit The rath may	A slight peterbial stamp tash is seen only in 20% of patients, in the skin of the antendateral surfaces of the body and limbt. Sometimes no- alescent bemorrhages appear in the lumbar
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Table I continued

	Hemonbagic sephratic-		: ,	Omsk hemorrhagic
	aeștritis	lever	magic ferer	lever
b) la the	From the 3rd-4th day	In 50% of cases there	Typical copicus	Bleedings from the
mocous	र्ज केंद्र टॉडस्डर केंद्र	are no bemorrhages	bemotthages from	more, gurns, utenus,
ಹೀವ್ಯಚಾಡ	are termorrhages in	from the note,	the note and gress.	gagroimenmal tran.
	the scleare, rescour	Hematemesis and	In SON of cases	etc. are mirequent
	ಪಾಲವರ್ನವರ ಈ ಚಿತ	intenial bloeding	there are bemater	and mild.
	oral cavity, and es-	श्रार रशार बच्चे विद्या है-	meses Ind melens,	
	pecially at the edges	4 days, Copions	which often endan-	
	of the hard palate.	personants occurs	ger the life of the	
	Hemoralizes from	∞ly in 10-15 ≤ cf	patiest.	
	the sase, guest and	putiests.		
	gastreintestical tract			
	are ture and mild.			
Resal	Marked decrease in	No distinct impair-	No impairment la dissett.	No impairment in Guresia
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	second and third pe-			
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	scate read failure.		!	
	During the reconvaler	l	•	
	cent period there is a			
	eistiact and prolonged	į		
	polymia and stebate.	ļ	•	
	Ecasu.		 	
Urtor	Typical albaninais	la the period of the	a the period of the	Codings in the period
Chieges	during the entire pe-	ಕ್ಷಣಿಸ ದೆ ಬೀ ಯೇ ಸೀ	beight of the Circuse	el height of the Es-
	ಗಂತೆ ಬೆಳೇ ಕೋರ್ತ. ಟ	the following are	ರ್ಲೇ ಶರ್ಣಾ ಸಿ ಪರ್ನ	ense include: a slight
	क्रेट प्रस्टानी कर्त क्रीति	typical: moderate	erate albamimais,	(up to 1%+ Albertian)
	ನೀಗಂತೆ (ಕರ್ಷ-9ಮಮೆ)	ಜಾಭಾ ! 🏎 ಪ್ರಾದಾಣ್ಯ	sed in the sedimest	read er belist cells,
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Table I continued

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	Hemothises be, with a	Crimean bemorthagic	Centry Principles	Crost for outlaged
	perfection	iever	that reset	lever
Pain in the	Regular early ap-	In the per-od of the	in the period of the	In some patients that
resal tegion	pearance and dis-	acignt of the dis-	height of the Jin-	Pasternatolan sign
	tial manifesta-	eare trequent oc-	ease the Paster-	may be weally point
	tions of the Paytern	currence of a	sabku siga mas	tive in the period of
	325k+ 1122 +5 a	pourse Perfer	be observed only	height of the disease
	periods of the dis-	ar's n sign	ia fen patients.	
	ease, and of a			
	typical tesder point	,		
	in the lumbar re-	,		
	Zion on pulpation		İ	
Blood	Tupical bemoconcen-	Hemorementar en	Is the period of the	In the first mays of the
eprates even	tration from the	is typical in the	height of discare	direne there may be
a)wmoglebie	I fact day of the Car			•
-	•	fant days of the	there is distract	a slight hemocostem
and makes see	eine Is the re-	desease. In the	hypochtomic ane-	tration in the second
அம்வரன	considered being	last days of th	mia, la serie par	hait of the febrile
	ದೀರ್ಣ ಪ್ರಭಾಗ ನೇಕ	penal three n a	ricasi bemeşlebin	period the bemostobin
	Crease in hemo-	reduction in the	2013 fell to 20-	level and enjurocyte
	इतिकास स्टब्स	samber of entar	25°, and the	count decreases some
	======================================	socytes and miles	pumbe of enth-	-51.
	Cytes, whealth to	bemegisbin level.	rectues to	
	the lower normal	la sense patients	1,000,000/mm3	
	limiu.	with severe bleed-	ar lawer.	
		ಪ್ರಾತ ರಚಾವಾಗ ಎವರ-		
		स्था स्था देतारीक		
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		55-43% and engine		
		rocytes to		
	1	1600,000/==3r		
b) the	Typical: I) indial	fastage as the per	Employers the New	Fradings in the period
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ke-keep ten	1,000∦⇔=3 i2	क्षेत्र देश प्रमा देशस्त्रता	the disease: dis-	eaver considerable
and the	the last period (I+	lesispess (2,3))-	teset leutopeau	les-openia (3,000)
leckoupte	3 &111, 2) ==>-	4,900), slight sea-	(to 1,30)-	5,000/mm ³), somer
ioraela	uqura lester	property with a mode	2,000/== ³),	times very severe (as
	Cyania medifica	erate bandlorm deft,	consuctable near	to as 1,200-1,400),
	garanti 10 000-	asto-expanda and	trapens (35-45°)	ರ್ನಡ್ಡಿ ಕಾರ್ಪಡಿಸಲಾಗಿ <i>ಕ್ರಾ</i> ಚ್
	نود ڏ⊴∼'((0,01	appearance of plan-	್ಯಾದ್ರಾ ಸ್ಥಾಜ ಬ್ರೀಕ್	a bandform shift to the
	ಖಾರ್ಣಗಳು	ma cells.	left, sænettmes	lett relaine haspbo-
	iosiemost in el		with procure cells,	Citora aprovipophilia,
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Table I continued

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	Hesiotikazik sepitotik sepitotis	Criminau hemorrhagiu Jewit	Cestral Asianhemore thiggs fever	Omsk nemocrhagic fever
	philia; b) appearance in the peripheral blood of plasma cells, frequently as high as 10% and more			
	In the shoot to be fire 30 feet to 10 feet t	In two period of the ho gir of the discale there is a moderate thromboyen a {0.1,0.0}.	In the period of the being and of the dry exicle a moderate thrombopeana (6),000,000 but sometimes a much more solutions (3),000	In the period of the height of the dis- ease, a slight throm-bopenia.
d) ESR	Typical slow ESR in the first three per riods and a modelful acceleration in the reconstalescent per riod (to 2011).	Typical stight accideration of ESR towards the end of the period of height of the disease (to 20-30 mm/nout).	Typical ESR to 33- S5 mm/bour dum ing the period of beight of the dis- ease.	Slight slowing down of ESR in the februle period and acceleration during the recomplement period (to 20-30 mm/bom).
Remiratory system lestom.	Atspired charges. In the first period there is a slight directa bronchain in some patients. At the end of the second period and in the third period focal promoves in may develop as a complication in some cases.	In the period of height of the disease of an homeon is may develop. At the end of the period of theight of the disease focal poeur minus may develop in 10% of caso.	ir some patients in the period of beignt of the dis- ease a diffuse acute birtishis may develop.	From the fare flags of the disease there is an acute bronchise. and in 31 % of cases specific focal pneumonia is noted. At the end of the febrile period a bacterial focal pneumonia buy appear as a secondary complication.
Gastro- intestinal tract lessons.	From the 3rd-4th day of the disease there is national, permittent womiting. Ion from certify history, epigatoric pain and tendersess on palpartion. The odor from the mouth is too pleasant. Hemanitement and blood in the stook are tare, Comblereding is rate, in some cases in the second and third period of the disease (4th-9th day) a dismall picture of faculte abdones may denote the wellog (semantica).	From the first days of the disease there is a marked fack in appetite, and increasing third. Vomiting, often with blood, in common. There is a heavy putred odor from the mouth. The absomer is soft, often different reace. Changes in the stools are topical. Tany or bloodinanced mools are tare.	sometimen almost	There is almost complete. List of apposite from in- first days of the disease. Not infrequently a gain and odor, from the moor. Names and vomiting at 33% of cases. Soft abri- domes only slightly tender on palgration.

Table I continued

	Hemorrhagic nephrotic- nephritis	Crinican hemorrhagic fever	Central Assan hemor- rhagic fever	Omsk hemorrhagic fever
	into the stomach and intestine water 1/2 the mesentery, pan- creas and perirenal tissue)			
Liver and spicen	At the height of the disease the liver in 50 of cases may be palpated and is moderately enlarged. The spleen is rarely enlarged.	There is slight enlargement of the liver and spleen during the period of height of the disease, approximately in 33% of patients.	In the period of height of the disease the liver is usually considerably enlarged (palpated at 4 cm below the costal margin).	In the period of height of the disease the liver is slightly enlarged and tender to palpation. Enlargement of the spleen not usual.
Nervous system lessons	Changes regular. From the first days u.ere is a severe headache in all patients. In 27.5% of cases from the beginning of the third period there is a merked state of stupor, mild meningeal symptoms, and weak pathological reflexes (Babinski and others). CSF is usually unaftered, the spinal fluid pressure is increased. One may observe distinct phenomena of serous meningitis. Rarely does one ser a clinical picture of meningo-encephalitis with distinct impair- ment of conscious- ness - stupor, delir- ium, psychometor excitation and some- times coma.	(Babinski and others). CSF is usually not al- tered.	From the first days there is headache, drowsiness and apathy. Rarely there may be a brief loss of consciousness and in severe cases a comatose condition. Meningeal phenomena and discrders of tendon reflexes are rare and not distinct.	From the first days of the disease the following signs appear: headache, limb pains. Manifestations of organic nervous system lesions (pathological reflexes and meningeal signs) are rare, brief and not distinct. In the Buku-inian variant of hemorrhagic fever the injury to the nervous system is more distinct. The following signs are very frequent: brief psychomotor excitation, aniso-reflexia, appearance of pathological reflexes. In one third of the cases there are meningeal signs

Table I continued

	Hemorrhagic neprrotice nephritis	Crimean hemorrhagic fever	Central Asian hemor- thagic fever	Crisk hemotrhagic fever
Metabolic disorders	At the height of the disease (second and third period) the following are typical: some hypoproteinemia, distinct arcremia, frequently high (17 to 200-100 mg from 100 mg from	Metabolic disorders are rare. At the height of the dis- eare and during the first day of the reconvalencent period there may sometimes be moderate atotemia.	At the height of the disease there is a mouerate hyporometric (2 to 0 to 2), mainly due to decrease in globulins and fibrinozen. During this time there is a regula tenderate hypogliceriae. A considerable decrease in the associate of the decrease in the associate of the blood is typical.	Changes in metabolism not regular. At the height of the disease one one serves only a moderate hypoproteinems and some lines slight arotems.
Compli- cations	One rarely observes massive hemoritages in the kidney (and tear of the kidnes) and in the epirenal parenchyma, with development of a clinical picture of "acute abdomen". Hemoritages in the mesentery and the wall of the intestines with development of an ileus syndrome; hemoritages into the stomach and other internal organs; acute insufficiency of the kidneys and development of a clinical picture of arotemic uremia, focal pneumonia, purulent parotivis and submaxilitis.	p-limonary) very rare. Focal pneumonia ob- served in 10-16 °C of cases. In some patients parotitis, epidelimitis and peritonitis develop.	Massive bleedings from the gastro- intestinal tract are very frequent and are a danger to life. In some cases a deep focal pneumenta develops. One very rarely observes inflammation of the salivary glands.	Fecal pneumonia both early (sirol) and late (bacterial) are very frequent. Otitis, parotitis and pselitis develop rarely.

Table II from [216]

Differential diagnostic signs of HNN and 'acute abdomen"

Signs and combinations	Clinical characteristics					
of signs	HNN	"acute abdomen"				
Features of abdomination pain a) origin	Abdominal pain appears on 3-5th day	Sudden onset of pain - the first clinical sign of onset of pithological condition (gastrointestinal perforations, acute peritonitis)				
b) intensity	Usually mild pains, never intract- able ("knife stroke")	Very acute pains ("knifing") frequent				
c) localization	Most frequently localized in epi- gastric region but may also be diffuse	Most often in epigastric region, but may also appear elsewhere				
d) combination with vomiting	Pains usually pr	recede vomiting				
e) combination with fever	Abdominal pains usually preceded by typical high temperature re- action	Pains usually begin while temperature still normal, temperature later rises				
Combination of abdom nall pains with other pain	Abdorunal pains usually combined with pains in the lumbar region	Lumbar pains only when a gastroducdena ulcer penetrates into the pancreas, in nephrolithiasis colic, or retroperitonea appendicitis				
Urine and diuresis changes	Characteristic	Not characteristic, occur rarely				
Blood changes	Characteristic (see other tables)	At the onset of pain attack blood may be normal, with neutrophil leukocy- tosis developing later				
Combination of pain syndrome vith other clinical signs	Abdominal pain confided with various symptoms characteristic of HNN (hemorrhagic cash, renal injury etc.)	Abdominal pains dominate clinical picture, often typical clinical manifes tations of acute peritonitis also appear within the first 12-24 hours				

Table III from [216]

Differential diagnostic signs of HNN, mosquito-borne Japanese encephalitis and tick-borne encephalitis

Signs	HNN	Mosquito-borne Japanese (autumn) encephalitus	Tick-borne encephalitis (spring-summer)
Period of maximum morbidity	Maximum morbid to in action 2	August-September	Amil·july
Epidemic features	No traces of tick bites	No traces of tick bites	Traces of tick bite are of diagnostic value
Consciousness	Persists in most patients	Most often impairment, often coma	Various degrees of con- sciousness impairment
Meningesi signs	Rare's Siersed, approx. in 5 % of cases	Usually observed die-	Usually observed, distinct
Encephalitis, pathological reflexes	Rarely observed, approx. in 5-10 viol cases, usu- ally disappears rayidly	Observed as a rule, tonic convuls. In character, the, central paraly, s (heromonoparese s, bulbar disorders	Observed as a rule. Neak, a ro, his paralises of neck numbers and threadic region, bulk as distorders, spartic pareses - less frequent
Cerebrosp.nal fluid	Usually not - Approx. in 5 % of cases moderate rise in protein, pleo- cytosis and sery rarely bloody liquor	Changes also Puring first days a rise or cell numbers, later - an increase in protein (up to 2.8), distinct cytosis (up to 200 cells per 1 mm ²	a,s observed
Blood changes	See above (ether tables)	Moderate leakocytous with a neutrophil shift to the left, ESR ac- celerated	Moderate leukocytosis, neutrophisia, aseosinophilia. ESR accelerated
Urine and diuresis changes	Characteristic changes (see above)	Changes not char- acteristic, some- times traces of procein	Changes not characteristic, sometimes traces of profess

Table IV from [216]

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The most important signs of the main forms of viral endemic hemorrhagic fevers (scheme of M.P. Chumakov, elaborated on by A.A. Smorodintsev)

	Hemorrhagic fevers						
Main indexes	HNN	Crimean	Central Asian	Omsk	Kyasanur Forest disease	Argentinias	
1. Properties of the virus							
Sultivation outside the human body	-		-	+	+	•	
sperimental infection in white mice	-		-	+			
Experimental infection (febrile reaction) in							
monkeys	-	+	-	+	+	+	
Antigenic relationship to tick-borne en-			1		1	ì	
cephalitis virus	-	-	٠ -	•	j +	-	
Susceptible animals with clinical (cl) or sub-		l	1	1	İ	l	
clinical (subc!) form	Vole	7	Rabbit	White	White	Guines	
•	İ	l	(subcl)	musk-	mouse (cl),	pig (c1),	
			ļ	128 (cl),	1 -	white	
		1	1	mouse	(c1)	Incuse	
	1	1	1	(cl)		(cl.	
ii. Epidemiology							
Seasons lity	Poly-	Spring-	Spring-	Spring-	Summer-	Autuma-	
•	seasonal	summer	nummer	ummer	autuma	winter	
Role of Izodid ticks as carriers and vectors of	1	1	1	l	1	ì	
the disease in nature	-	+			į +	-	
Participation of Gamasoid mites in the circu-	ļ	1	1	[1	İ	
lation of the virus in mice-like rodents .	+	-	-	• •	-	+	
Transmission of the virus to man by rodents	1	1	1	1		1	
or their ectoperasites	+	1 -	-	-		+	
III. Clinical picture	1	1					
Incubation period (days)	11-24	2-4	3-4	3-7	4-8	9-14	
•	1	(M.P.	Į	1	1	1	
	1	Chuma	- [ĺ	1	l	
•	1	kov),7-	1	1	1		
	1	10(E.A.	.]	1	1	1	
	1	Cal'-	1	1	1 .		
		perin;	1	1	1	ì	
Diphasic temperature curve	ł -	1 *		-	•	-	
Diphasic fevers	1 -	1 -	-	'+'	•	-	
Marel and uterine bleeding		•		*	+	1	
Gastrointestinal bleeding	1 *	+	**	1 *	-	1 *	
Severe renal pathology	. ↔	į .	1 -	1.	-	*	
Memorrhagic rash	· [•	1 *	**	į -	-	1	
Condition deteriorating after decrease in	1	1				1 .	
temperature		-	1	-	1	1	
Leukocytosis and increase in number of	1.		1 -	1 _	1 _	1.	
Tork's cells	• •	1:	1.	1.	1:	1:	
Leukopenia, shift of blood formula to the left	3-5	3-5	10-30	0.5-3	ŧ -	18	
Lethality (%)	,,,	3-3	1	0.53	1 7.0	1	
IV. Main preventive messures							
Vaccination	j -] -	-	+	1 •	j +	
Deratization and distafection	1.	1 .	1 .	1 -	١.	1 .	

Most cases occur in the fall and early winter (October and November) and blood in the urine has been reported in all cases [18, 278]. Chicken erythrocytes, the aldolase reaction, and special complement-fixing antigens have been tested as diagnostic media. L. A. Vereta and T. P. Yur'yeva reported on the demonstration of complementfixing antigen in Omsk-fever patients when convalescent serum was the antibody source. The antigen was detectable up to the twelfth day after infection and could be demonstrated both in vitro and in infected tissue culture from reactions produced by yellow fever and several simian viruses [265]. Since the lytic reaction was clearly demonstrable in only 57--60% of test cases, it was recommended as an auxiliary test rather than for differential diagnosis [87, 144]. Results of the aldolase reaction proved entirely satisfactory for the differential diagnosis of HNN [204]. Since viremia was present in animals with an experimental infection for 23 days, it was concluded that apparently healthy animals or convalescing animals were the principal vectors of the disease in an epidemic area [284]. Omsk-fever virus produces an extensive cytopathic effect in susceptible swine-embryo kidney cultures; RNA-containing inclusions and viral antigen are easily demonstrated by tle FAM [94].

Serotherapy methods were compared by Rodin et al. and were found to be only moderately effective [190].

In general, diagnosis of HNN is difficult as the clinical sumptoms are so similar to those of other diseases and because, when the disease is suspected, comfirmatory diagnosis is difficult and time consuming. Smorodintsev [216] suggests that, in view of these difficulties, the patient should be questioned extensively as soon as possible so that his contact with vectors may be established or disproved. Hemorrhagic fevers are naturally focal diseases with foci in the Rostov, Bulgarian, Western Siberian, Khabarovsk, Moscow, and Amur regions [18, 30, 88, 172, 277, 278]. High humidity and the proximity of the population to swampy areas affects the mortality rate [18]. Mild cases may be undetected or misdiagnosed, while acute cases may be fatal [278]. The red field mouse, rats, other mice, voles, and muskrats have been carriers in various epidemics and an increase in the forest-mouse population seems to herald outbreaks. Because of the diagnosand therapeutic difficulties, extensive prevention involving frequent land clearing and vigorous antirodent programs is practiced [88, 277, 278].

II. HOOF-AND-MOUTH DISEASE

Hoof-and-mcuth virus enters the bloodstream rapidly, penetrates organs, and disrupts normal hematopoiesis. Changes in virulence were found to be linked to changes in penetration properties and multiplication capacity. Viruses whose virulence has been attuated by passaging penetrate the blood and organs less easily and multiply with difficulty [78, 272].

Investigations have shown that various tissue cultures are suitable for the cultivation of virus for diagnostic and vaccinal use. Bovine epithelium [148, 243], swine kidney, and newborn rabbit tissues [102, 206, 235, 245] have all proven satisfactory for these uses. Footand-mouth virus has a complex immunological structure and therefore, many diagnostic tests for the disease can be used [195]; these include complement fixation [155, 215], virus neutralization [242], and diffusion precipitation in agar [166]. Skomorokhov [215] recommends complement fixation, which can be used to evaluate vaccine potency.

Techniques for the preparation of virus-containing tissue which the Soviets have found effective are the use of Ascangel [24], chloroform [102, 272], freon [272], and the mincing of freeze-dried rather than wet tissues [116, 161]. A combined treatment with freon, n-butanol, and chloroform removed 98-99% of tissue proteins without lowering the original virus titer [272]. Adding the purified virus to fat-free milk and spray drying at $30-35^{\circ}$ C is a convenient drying method. When stored, the virus had a shelf life of 1 year at $17--25^{\circ}$ C when its residual moisture content was 6-9%. No change in storage properties was observed when the moisture content was reduced to 1.3-4.4%. This extra-dry preparation could then be stored at 37° C for 60 days without loss of activity [71, 161].

Attenuated and dry hoof-and-mouth vaccines have been successful in large-scale use. A dry adsorbed vaccine which is 99% effective had been tested on 3.5 million sheep as of 1963. An attenuated vaccine which protects up to 9 months is also in use [215]; the dry vaccines usually immunized for 2-6 months [117]. A dry vaccine prepared from strain L-III was tested on cattle. Its preliminary success and low allergenicity have recommended it for wider use [176].

III. RABIES, AUJESZKY'S DISEASE, AND POLAR MADNESS

Rabies and "polar madness" or "rage" (Tundra rabies) of arctic animals, especially foxes, and Aujeszky's disease or "pseudorabies" are viral diseases that affect wild animals primarily. Humans are susceptible to rabies and possibly to rage virus but not to Aujeszky's disease virus [254]. The table presents criteria for distinguishing rabies from Aujeszky's disease.

Table V
Differential diagnoistic criteria for Rabies and Aujeszky's disease

DIAGNOSTIC SIGN	RABIES	AUJESZKY'S DISEASE
Reaction of virus to drying	weakens	quite resistant
Location of virus in the body	nerves	blood and lymph
Infectivity of sali- va	always	not in the absence of nasal discharge
Infectivity of blood	sometimes	yes
Behavior of virus on being heated to 60°	killed in 5-10 min	killed in 30-50 min
Babes-Negri bodies	present	absent - acidophilic inclusions seen in spinal ganglia of cattle
Incubation period	days to weeks	always short
Prodromal period	several days	absent, rapid onset of disease
Aggressiveness in the affected animal	marked	absent
Scratching	rarely	as in swine
Drooping of lower jaw	often	seldom
Quick death	seldom	often
Susceptibility of humans	yes	no
Oral infection	no	yes
Virus in the paren- chymal organs	ne	,,32

Table V continued

Means of spreading the disease

biting

by contact and in food

Taken from: Orlov, F. M., Comp. Virusnyye bolezni zhivotnykh (Virus diseases of animals) Moskva, Selikhozizdat, 1963, 163-164.

"Rage" has been observed in wild and domesticated polar foxes [39, 90, 104, 105, 106, 235, 236], wolves, dogs, deer, bear, elk, and lemmings [235]. It is believed that the mortality rate is over 90% and that lemmings form a natural reservoir of this disease and spread it to foxes during their migrations [235]. These foxes probably infect domesticated dogs. Immunological and serological tests show that this virus is similar to but distinct from rabies and all other neurouropic viruses [89, 90, 104, 105, 235]. Specific antibodies to "rage" are found in the blood of foxes surviving an asymptomatic form of the disease [89]. No Babes-Negri bodies were observed in any case, although unidentified intracellular inclusions were found in for neural tissue taken from experimentally infected animals [106].

One human victim has been reported [90]. In the Nov.-Dec. 1961 outbreak in the Yamal region, a child was bitten by a fox. The child died 25 days after being bitten, despite treatment with antirables serum. Post-mortem examination of both the human and fox tissue revealed no Babes-Negri bodies; "rage" was therefore given as the cause of death. Serological methods employing complement-fixation and virus neutralization show that this virus is related to Aujeszky's virus and infectious equine encephalomyelitis virus as well as to rables virus [235, 236].

No data on any diagnostic methods faster or more accurate than those mentioned have been discovered in the literature. Unconfirmed reports of the effectiveness of antirables gammaglobulin in neutralizing this virus have been published; claims that preparations made from this virus will prevent rables have also appeared [235]. Rables vaccine will protect foxes aga ist "rage" virus but no cure is known for the disease once the symptoms, similar to those of rables, appear. Therefore, prevention of contact between wild and domesticated animals is the only effective

means known for checking the spread of the disease [235]. Animals whose winter rations contain added minerals possess slightly more resistance than animals fed a standard diet [235]. Wild and domestic rodents and their ectoparasites are considered the principal reservoirs and vectors of pseudorables or Aujeszky's disease, and fleas and ticks are the actual mechanical vectors [254]. The carrier state can last as long as 100-130 days in fleas and the disease can run its full course in 2 days in livestock, dogs and cats [254]. This shorter incubation period is one of the signs that differentiates this disease from rables (see Table V). The disease is sporadic, usually occurs in the fall, and generally kills young animals [254]. Efoassay, histology, and diagnosis by clinical symptoms are teing replaced as diagnostic methods by the more rapid immune reactions, diffusion-precipitation tests and, most recently, the fluorescent-antibody method (FAM) [32, 101, 170, 222]. The diffusion-precipitation-in-agar reaction is rapid, inexpensive, and simple to perform. Its suitability for general use is subject to proof of a lack of additional nonspecific reactions [22]. To date, the FAM is the fastest and most accurate method; the appearance of viral antigen can be detected 2 hours after infection of a chickembryo tissue culture [3]. The types of vaccines in use are: a specific gammaglobulin which is obtained by alcohol precipitation at low temperature [124], to which killed virus is added, a chick-embryo tissue-culture vaccine in which the virulence of the virus is decreased by long passaging [213, 242], a similar vaccine prepared from virus passaged on mouse tissue [242], hyperimmune serum, brain homogenate [254], and a vaccine prepared in Czechoslovakia from a weakly virulent, freshly isolated strain The last vaccine, still experimental, was announced [214]. in 1964. The virus was suggested as a possible vaccinal strain; if it is, the need for long passaging [87] to obtain sufficiently attenuated virus would be eliminated. Challenging vaccinated laboratory animals with the wild-type virus showed the efficacy of all the vaccines tested. In addition, specific gammaglobulin alone protected newborn pigs with an immunity that lasted for three weeks 4]. Passaged virus was used in large-scale tests and was the most effective among thousands tested. Only a few animals died [213]. "SUCH-1," the viral strain isolated in Czechoslovakia, protected test animals as well as a passaged strain [214].

Examination of rabies vectors covered rodents,

including bats, and emphasized canines. Stray dogs are the principal vector in civilized areas. Wild foxes are considered the principal reservoir of the disease, spreading it to dogs. A survey has shown that pigs and birds also carry the disease [157]. Strains of rabies virus isolated from wolves and dogs are the most virulent and the least virulent strains come from humans, simians, and livestock [157]. Immunofluorescence and the FAM are used to determine specific antigens for differential diagnosis of rabies. These methods are both faster and more accurate than diagnosis by clinical symptoms, histology, and bioassay [218]. The FAM permits visual localization of antigen and cytomplasmic inclusion formation in living cells [196], and when the dye is bound to hyperimmune donkey serum, it is the most useful method for differential diagnosis of rabies [120, 192, 221].

Since some of the most effective rabies vaccines are difficult to prepare and maintain and have dangerous side effects, both tissue cultures and various viral strains are being screened in the search for suitable replacements for antirabies gamaglobulin and brain-tissue vaccines. study of rabjes virus variants showed that after long passaging in tissue culture the original wild-type strain acquires a shorter incubation period before causing symptoms and requires a lower Dlm (intracerebral) for infection of rabbits, but is completely apathogenic in rabbits when administered subcutaneously [158]. Variants of standard strains have been obtained; some of them are more pathogenic than the wildtype, producing symptoms in 1--2 days but with no discernable Babes-Negri bodies, while others cause atypical clinical forms of the disease. Especially interesting are strains isolated from African dogs suffering from a rabies-like disease related to Arctic "polar madness" or "rage," strains from cattle suffering from a disease described as "plague," and miscellaneous atypical strains from human adults [158]. When several variants were tested on different arimals! tissues it was shown that homologous immune sera were the most accurate for diagnostic purposes [192]. These results have prompted research into different virus strains and substrate tissues for vaccine preparation.

Since passage in a given animal brain-tissue culture increases the virulence of the virus for that particular species and lessens it for other species, and since route of administration alters the clinical course of the

disease [153], it is likely that a variety of tissue-culture vaccines will become standard for these reasons and because cost and production technology will be simplified.

A specific gammaglobulin obtained from vaccinated humans was slightly effective but was inferior to horse-serum globulin [76].

Rabies virus has been cultured successfully on chickembryo fibroblasts and an effective vaccine has been prepared from this culture [197]. Allergic reactions are one of the principal disadvantages of rabies vaccines in current use and several papers were published between 1962 and 1965 on experimental vaccines with reduced allergenic and anaphylactic proerties [31, 160, 210, 239]. Partial proteolytic hydrolysis of crude globulins during production reduces production volumes with increased vaccine yield [160]. Vaccine prepared from newborn rat and rabbit brain causes fewer allergic reactions than vaccine prepared from adult rat brains [31, 256]. Donkeys have been suggested as a source of antirabies gamma globulin since immune serum can be obtained from them more rapidly, their serum causes fewer reactions in use, and the animals themselves are easier to maintain and manage than horses [192].

Challenge tests of various vaccines and vaccination schemes have been reported in the literature. Production of active-passive immunity in laboratory animals has been achieved by the administration of a combined dose of antirabies gamma-globulin and 0.5% vaccine. Interference was eliminated by doses of gammaglobulin 4 days before starting the vaccination program [163]. The injection of cortisone interfered with the immune reaction, allowing a marked increase in virus multiplication [212]. Other experiments gave similar results [162, 210, 211]. The injection of standardized Fermi (formol) vaccine with or without gamma-globulin produced a plasmacytic reation in test animals, intensified RNA synthesis, and increased antibody titer in the resistant animals [211]. There was a direct relationship between the serum antibody titer and degree of resistance in the animal which, in turn depended on the potency of the vaccine [162, 210, 211].

At a conference on the effectiveness and safety of nonallergenic rabies vaccines held on the 18th and 19th of March 1965 at the Ivanovskiy Institute of Virology of the Soviet Academy of Medical Sciences and sponsored by a com-

mission of the Ministry of Public Health, all particir ints agreed that nonallergenic vaccines should replace the standard Fermi vaccine [210]. This special commission was established in 1962 especially to investigate the properties of new preparations and to engage in large-scale tests of them. Both wet and dried vaccines were tested by various laboratories and agencies. Members of the commission were: R. M. Shen, Institute of Virology; O. G. Andzhaparidze, head of the State Control Institute for Medical and Biological Preparations, Ministry of Public Health; S. S. Unanov, director of the Moscow Viral Preparations Research Institute; M. A. Selimov, head of the Rabies Laboratory at the Institute of Poliomyelitis and Viral Infections, AMN SSSR; M. A. Khiyenenson, Moscow Municipal Sanitary-Epidemiological Station; A. S. Makaryan, senior inspector of the Ministry of Public Health RSFSR; A. A. Mtvarelidze, Tbilisi Sanitary-Epidemiological Station, and B. A. Kantorovich, senior scientist of the Institute of Virology. V. M. Zhdanov, director of the Institute of Virology, was in charge of the organization of the work [210]. The commischarge of the organization of the work [210]. sion began its work in January 1963, and made the following recommendations to the Ministry of Public Health SSSR in 1965: 1) immediate introduction of the nonallergenic vaccines into medical practice; 2) broader use of the dry nonallergenic vaccine; 3) the establishment of a similar commission to carry out more detailed studies of such vaccination programs [210].

IV. SWINE PLAGUE

Swine plague causes extensive damage to the circulatory system as s'own by extensive septicemia in infected animals. Secondary infections such as paratyphoid, bacterial hemorrhagic septicemia, diplococcal infections, and listeriosis are the principal dangers of this disease. Differential diagnosis is complicated by the lack of really reliable laboratory tests. Likhachev states in Virus Diseases of Animals that the only definite means of differential diagnosis are analysi. of clinical data, results of bacteriological studies, the epidemiological characteristics of the local outbreak, and the final isolation of the agent and production of the disease in animals [118]. Most vaccines are derived from infected tissue cultures and are concentrated by treatment with freon and subsequent precipitation in acetone [34]. Virus passaged in tissue cultures (usually swine embryo) differs in virulence from the original virus. Several passaged strains retained their virulence but were not immunogenic. However, these strains were used to produce hyperimmune sera and subsequently to inoculate other tissue cultures from which an avirulent dry vaccine was prepared for administration by aerosol. This aerogenic vaccine required seven days to become effective and protected 100% of test animals for two months [33, 152, 153, 251].

V. VENEZUELAN EQUINE ENCEPHALOMYELITIS

A fluorescent antibody test and a specific hemagglutination test based on recent discoveries have been suggested as possible diagnostic methods for Venezueland equine encephalomyelitis (VEE). In an investigation of virus reproductive dynamics in 1965, Gaydamovich and Vagzhanova discovered that a positive hemagglutination reaction can be obtained in tissue culture during the beginning of the logarithmic growth phase (6--7 hours after infection), and that there is a "threshold of infectivity" below which a positive hemadsorption reaction is not obtainable. They suggested that the hemagglutinating properties of the culture fluid would be useful for the early diagnosis of the disease and for studies of viral growth dynamics [279].

A diagnostic test for VEE based on the early appearance of VEE virus hemagglutinin in tissue cultures was devised by Gaydamovich and Vagzhanova. A comparison of results showed that neutralization indices were higher with tissue cultures than with convalescent sera and that the indices were 10,000 times lower when the cytopathic effect in mice was determined than when neutralization was performed with immune rabbit sera. Results could be obtained within 18 hours, and the method was recommended for early diagnosis of the disease [69]. The fluorescent antibody method (FAM) is also used in the study of viral reproduction and it has been modified for diagnostic use. Actinomycin D selectively halts cellular, but not viral, biosynthesis [280]; the acceleration of viral reproduction in tissue treated with the antibiotic has been reported once cellular DNA synthesis has ceased, the FAM [291]. is employed to determine the synthesis site of VEE virus. RNA precursors and viral antigen can be detected visually in the cytoplasm by this method [280]. In the second method, when viral reproduction in tissue culture is accelerated by actinomycin-D, hemmagglutination tests can be used earlier than when the suspected culture is untreated [291].

Chemical inhibition of viral attachment to the cell membrane is reported by N. V. Kaverin. In his study, mouse fibroblasts and human liver cells in culture were treated with uranyl acetate which inhibited phosphategroup activity of the cell membrane. VEE virus attached to the cells but was easily removable, suggesting that phosphate groups are necessary for the firm binding of VEE virus to cell surfaces [100].

VI. MISCELLANEOUS DISEASES OF LIVESTOCK AND HUMANS

Insects and contaiminated food and water are the principal sources of vesicular stomatitis, a disease which infects cattle, swine, and humans (the latter under laboratory conditions). Some of the principal mechanical vectors are: Storage and restrance, and miscellaneous flying insects. Complement-fixation reactions are commonly used for differential diagnosis. Surviving animals are immune for one year after recovery. No specific therapy was reported in the literature studied and the most common treatment is symptomatic [132].

In the Soviet Union, irfectious equine encephalomyelitis is spread by ticks, flies, and mosquitos. The mortality rate is often 100% and Babes-Negri bodies are frequently seen in brain tissue of dead animals. Several papers have been published investigating its connection with rabies [206]. The two nost common diagnostic methods are bioassay and serodiagnosis (complement-fixation). Although therapeutic use of immune serum has been successful, the resultant protection is only transitory; this method has been replaced by vaccination with a chick-embryo vaccine (used on at least 45,000 horses as of 1963) or by an attenuated live vaccine obtained from rabbit brain [206].

Infectious equine anemia is spread in a variety of ways, generally from infected to uninfected horses via contaminated food or by Diptera Transmission by intestinal parasites is also suspected. After recovery, an animal can carry the infection up to 6 years. Differential diagnosis is difficult since there are several diseases with similar symptoms, and chemical diagnostic methods are often unreliable. Diagnosis is mainly based on observation of symptoms and on the fact that outbreaks usually occur in late summer--early fall. Formol and aluminum hudroxide vaccines are often unsatisfactory; quarantine is thus the only really effective preventive measure [191].

Japanese infectious equibe encephalomyelitis, a disease usually called "Japanese-B"encephalitis when observed in humans, also displays seasonality. It is most common near swampy areas during the summer, when it is spread by infected horses. Transovarial transmission has been demonstrated in the following ticks which are the principal vectors during the winter months: Terrisential Fictus L. Natt 111, Inches michalo, Rhip, ciphilus turnicus, R. burs. Rhiphicephilus singuirous, hy lemma isinticum.

W. Ir resultar, 1/2 in the most common diagnostic method. Recovery confers immunity in animals. Administration of formol vaccine (in three shots) each year before the start of the epidemic season, is effective as a vaccination program, although insect eradication is considered to be the most effective control measure [208].

Contagious pustulant dermatitis of sheep and goats (contagious ecthyma) has been reported in humans, including volunteers for experimental infection and individuals infected by a diseased animal. The disease affects mainly young sheep and goats, is spread by contaminated food and water, and has an incubation period of 8--10 days. It may be diagnosed by clinical observation, by the agglutination, precipitation, and complement-fixation reactions, by neutralization, and by bioassay. A dried vaccine, administered in saline, has been developed which protects against experimental and natural infections. Sheep are immune following recovery from natural infection. In the limited studies involving humans, little or no immunity existed after recovery and the vaccine gave limited protection [234].

Cattle are most susceptible to Rift Valley fever and are infected by insects which carry the virus from its rodent reservoirs to its principal hosts. Humans usually acquire the infection from infected cattle, and the mosquitoss dedes caballus and Culex fheileri. Other vectors are the fly Eretrapoidites chryscgaster and the Rhiphecephalus spp. tick [231]. Standard serological reactions are used diagnostically and several experimental live-virus vaccines have been tested [231].

Livestock, particularly cattle and their wild relatives, are the most susceptible to rinderpest. The domestic animals acquire it from contact with wild carriers which include rodents, wild birds, insects, and pigs, as well as dogs and cats. The suslik Citellus rengelicus is the principal reservoir and carrier [21]. There are numerous papers reporting the results of studies on the serological relationships of this virus to various simian and swine-plague viruses. In the Soviet Union, complement-fixation employing specific hyperimmune serum or viral antigen arrations is used for early diagnosis. The diffusion precipitation-in-agar reaction is commonly used for differential diagnosis [21].

Most current research published deals with studies of various viral vaccines. A formol-aluminum hydroxide vaccine has been reported to be more effective than the tissue vaccines used previously, and a live-virus vaccine (attenuated) produces an immune response within 24 hours [21]. The use of ultrasound does not inactivate lapinized vaccines unless application is prolonged (60--120 min); small doses are useful in separating the lapinized virus from the tissue culture [167]. A dry vaccine prepared from stabilized Nakamura-III (L-III) strain proved as effective as the standard formol vaccine; however, its peak immunization titer required 20 days to appear [241].

VII. POX-VIRUS INFECTIONS AND THE DEVELOPMENT OF EFFECTIVE VACCINES

Pox viruses grown in tissue culture have been employed in vaccine reserch and in studies of the synthesis and intracellular localization of DNA. The reactivation of heatkilled viruses of this group by closely related strains has been studied and the results of one such study are shown in Table 6.

Table VI from [33]. Reactivation between various, vaccinis and optromelia viru. 16

Insotivated virus			Tested in		
	Reactivating virus	Control	rabbits (scarifi- cation)	chick embryce (chorio- allantois)	mice (intra- plantar- ly)
Vaccinia (asuro-	Variola	Vaccinia.	NV	NV+VA	
Associate)	i	mactivated	0	0	_
]	Vaccinis, active	NV	. NV	_
	•	Variola, active	0	VA	
Vaccinia.	Alastrim		NV	NV+AL	
(asero- vaccisis)	1	Vaccinic,	!	_	
		inactivated	0	. 0	_
		Vaccinia, active	. NA	NV	
		Masicula, access	i 0	AL	
Ectromelia	Alestrim			EC+AL	EC
		Ectromelia,	Í	1	_
		inactivated	. -	1 0	0
		Ectromelia, active		, EC	EC
		Alastrim, active	• —	AL	0
Alestrica	Ectromelia		: <u> </u>	AL+EC	_
		Alastrim,	ì	•	
		inectivated	-	. 0	
		Alastrim, active	• —	AL	
		Ectromelia, active	-	£C	
Ectromelia	Vaccinia	Ectromelia.	_	EC+OV	EC
	1	inactivated	! _	. 0	0
	Ì	Ectromelia, active	i _	EC	EC
	1	Vaccinia, active	-	NV	o
Vaccinia	Ectromelia	Ma a fa i	NV .	NV+EC	_
(aedro- vasolisia)		Vaccinia, inactivated	;	0	_
		Vaccinia.	-	i	
	1	active	NV	NV	
	i	Ectromelia, active	0	EC	! _

NV - lesions characteristic of vaccinia (neurovaccinia strain)

VA — lesions characteristic of variols
AL — lesions characteristic of alastrim
EC — lesions characteristic of ectromelia

^{0 —} no lezione.

In this study [36], the authors demonstrated reactivation using vaccinia, varicia, alastrim, and ectromelia viruses. Results published in later papers indicated that reactivation of a heat-killed virus depends on the integrity of its DNA and part of its protein component [37], and that the factor causing deproteination of viral neucleocapsids is coded in the cell genome rather than that of the virus and that effects of this factor are observable within 2--2 1/2 hours after infection [151]. Reacitvation does not occur in cell cultures lacking this factor. Autoradiography and the FAM (fluorescent antibody method) have been used extensively in the study of cell-virus interaction and for differential diagnosis [80, 149], and autoradiography has been employed in studies of early viral DNA and antigen synthesis [175]. The FAM detects specific viral antigens in tissue cultures within 6 hours and has been used to distinguish vaccinia, variola, alastrim, varicella, cowpox, Herres zister, and Herres simplex viruses. The chief advantages of the FAM are its specificity and simplicity [80]. Using cytopathic effect in tissue culture as part of the diagnostic procedure was complicated in one case by lack of temperature control; the importance of controlled. optimum temperatures during culture incubation was stressed as cytopathic effects often were not observed at temperatures higher or lower than optimum [79]. Because of their sensitivity, standard tissue-culture methods were generally recommended for confirming diagnosis and for diagnosis of asymptomatic carriers [133]. The two variants of vaccinia virus most commonly used in the preparation of vaccines have been called "red" and "white" because of the pockmarks they produce on chick chorioallantoic membranes. Differentiation is therefore done visually and confirmed by the differing hemagglutination activity of the two variants [133].

Antiviral compounds such as 6- azauracil riboside and urethane delay mortality in mice infected with vaccinia virus intranasally and intracerebrally, but do not lower mortality rate [86],

Tissue cultures are used to evaluate the activity of strains being screened and the potency of viral preparations, and to select mutants for further screening [81]. The plaque-forming properties of vaccinia virus in chick tissue culture have rendered it useful for a rapid, accurate, and economical procedure for determining vaccine potency. The method employs test-tube cultures and gives easily interpreted results in 48 hours [81].

Clonal mutant vaccines have been prepared in tissue culture and these vaccines have successfully immunized test animals and children [227], although they possess atypical properties in comparison to the parent strains and the heterogeneous virus population from which they were isolated [135]. Heterogeneous vaccines displayed properties dependent upon the proerties of their most common component [135]. The interference of inactivated virus with the multiplication of live virus in tissue culture has been traced to an as-yet-unidentified factor located in or on the inactivated virus. One of the principal factors governing the effect of the inactivated virus on live virus multiplication is the time between the injection of each type [174].

The immune mechanism involves plasmacytic response. In a series of papers [136, 225, 226, 229] the authors demonstrate the important role of phagocytosis, the significance of the site of inoculation and the innoculum dose intravenous and intranasal are the most effective routes and intranasal is most economical inoculation method), and the degree of antibody synthesis in immunologically competent cells of the lymphatic organs. Antibody titers are highest after intravenous inoculation. The duration of immunity depends on the degree of plasmacytic response over a period of time and not necessarily on the initial degree or response [225]. Data from an experiment performed in 1962 confirm the above conclusions. In this experiment, animals irradiated with sublethal doses of gammaradiation were immunized with a dry live-virus vaccine 6--10 days after irradiation. In most cases the radiation slowed the development but not the degree of immunity. These results differ from those obtained with killed vaccines and from those obtained in experiments in which previously immunized animals were exposed to ionizing radiation [56].

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APPENDIX I.

SUPPLEMENTARY BIBLIOGRAPHY OF ARTICLES AND BOOKS CONCERNING DIAGNOSIS, THERAPY, EPIDEMIOLOGY AND MISCELLANEOUS STUDIES OF VIRAL DISEASES PUBLISHED BETWEEN 1962 AND 1965. LISTED ALPHABETICALLY BY AUTHOR.

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APPENDIX II.

REPORTS OF CONFERENCES ON VIRAL DISEASES HELD BETWEEN 1962 AND 1965 AND THEIR PARTICIPANTS

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 Subject discussed at the Conference on the Use of
 Antibiotics held in Moscow 1963. Antibiotiki, no.
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- 3. Belikov, G. P. Conference of the Presidium of the I. I. Mechnikov All-Union Scientific Medical Society of Epidemiologists Microbiologists and Infectious Diseases Specialists held 8 October 1965. IN: Akademiya nauk Kazakhskoy SSR. Vestnik, no. 9, 1966, 150.
- 4. Bychkova, M. V. Seventh Joint Scientific Session of the Poliomyelitis and Viral Encephalitis Institute of the Soviet Academy of Medical Sciences and the Byelo-russian Institute of Epidemiology Microbiology and Hygiene devoted to a discussion of the problem of tickborne encephalitis. IN: Akademiya meditsinskikh nauk SSSR. Vestnik, no. 1, 1964, 89.

Participants: Chumakov, M. P., Gilmanova, G. Kh., Gorchakovskaya, N. N., Karpov, S. P., Karpovic Panov, A. G., Pivanova, G. P., Robinson, I. A., Rzhakhova, O. Ye., Sarmanova, Ye. S., Serjeyeva, G. I. Shalunova, N. V., Smorodintsev, A. A., Stepanova, L. G., Vereta, L. A., Votyakov, V. I., Zasukhina, G. D.

- 5. Kats, L. N. Problems of biology and medicine discussed at the Thirteenth All-Union Conference on Luminescence held in Kharkov from 25 June to 1 July 1964. IN: Akademiya nauk SSSR. Izvestiya. Seriya biologicheskaya, no. 2, 1965, 319.
- 6. Kats, L. N. The Sixth Session of the Interdepartmental Scientific Methodological Commission on Anthrax Control held in Mcscow 12--14 March 1964. Zhurnal mikrobiologii, epidemiologii i immunobiologii, no. 2, 1965, 156.

7. Veber, L. G. Proceedings of the Second Scientific Practices Conference devoted to the activities of sanitary epidemiologic centers of Sverdlovsk and its environs. Gigiyena i sanitariya, no. 7, 1964, 124-125.

- 8. Yerkhov, I. S. Joint Scientific Session on Vascular and infectious Diseases of the Nervous System held 9--12 December 1964 in Sverdlovsk. Zhurnal nevropatologii i psikhiyatrii, v. 66, no. 5, 1966, 791-792.
- 9. Fourteenth All-Union Conference of Epidemiologists and Microbiologists and infectious Disease Specialists held in Moscow from 29 June to 4 July 1964. Zhurnal mikrobiologii, epidemiologii i immunobiologii, no. 12, 1964, 3.

Participants: Alisov, P. A., Belikov, G. P., Sokolov, M. I., Timakov, V. D., Vashkov, V. I., Yelkin, I. I.

- 10. Ninth Scientific Session of the Poliomyelitis Institute. Voprosy Virusologii, no. 1, 1965, 121-126.
- 11. Seventeenth Scientific Session of the Institute of Virology im. D. I. Ivanovskiy of the Academy of Medical Sciences, USSR. Voprosy virusologii, no. 1, 1965, 119-121.
- 12. Zeytlenok, N. A. Poliomyelitis and other enterovirus diseases. IN: Akademiya meditsinskikh nauk SSSR. Vestnik, no. 3, 1964, 94-96.

In 1963, the Eighth Scientific Session of the Institute of Poliomyelitis and Virus Encephalitis of the Academy of Medical Sciences, USSR, was held in Moscow. Four hundred and thirty-nine scientists from 45 cities in 14 Soviet republics, 21 scientists from seven Communist countries, and two American virologists participated in the session.

The conference dealt with problems of eliminating poliomyelitis, poliomyelitis-like diseases, non-poliomyelitic enteroviruses, latent oncogenic viruses, the impro ement of live poliomyelitis vaccine, the nature of viruses, and their relationships with the cell. Twenty-six reports and talks were given on the study of the nature of diseases

observed after mass immunization similar to the mild forms of poliomyelitis and expressed in the form of a brief paresis of the lower extremity, not uncommonly recorded under the clinical diagnosis of "poliomyelitis" or "myelitis." The Session indicated the need for investigators to concentrate their attention on determining the nature of the flaccid pareses of undetermined etiology from the viewpoint of the possible role of Coxsackie A viruses, adenoviruses, new, still unknown viruses, as well as agents or factors which are not viruses. Serological studies with Coxsackie A virus strains adapted to tissue cultures, with antigens of other enteroviruses as well as adenoviruses, should be carried out on a broader scale and, depaending on the results of the investigation of paired sera, methods of isolating the viruses in suckling white mice should be used.

The Session recommended that the Ministry of Health, USSR, record and take into consideration the polyiomyelitis-like cases as "flaccid paresis of undetermined etiology." It is essential that in the case of these diseases as well as in cases suspicious of poliomyelitis, clarification of the diagnosis with a final recording of the diagnosis be made by commissions of authoritative specialists consisting of neuropathologists, specialists on infectious diseases, virologists, and epidemiologists. The Session also considered it necessary to organize qualified virological and serological studies in every case of a disease suspicious of poliomyelitis as well as of all cases of flacid paresis of undetermined etiology.

The Session indicated the expediency of 1) determining the list of laboratories which can perform the necessary and adequately qualified virological and serological studies for poliomyelitis, the ECHO viruses, and Coxsackie viruses; 2) dividing the territory of the USSR into regions, assigning them to the nearest virological laboratories according to the list mentioned, and in the absence of such laboratories, assigning them locally to the laboratories of large central institutes; 3) giving aid to the laboratories in the matter of equipment, and the creation of the required conditions for carrying out the work on the necessary scale.

At the Session, 48 reports were presented on the problem of nonpoliomyelitis enteroviruses and the diseases which they cause. A study was made of different types of interaction of enteroviruses with one another and in combination with infectious diseases in human beings and animals, and processes of variation of Coxsackie A viruses on their adaptation to different tissue cultures.

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Seventeen reports presented the results of a complex study of latent tumor viruses, chiefly the OV40 virus (simian vacuolating), which can be found in virus vaccines. Frequent infection of Macacus rhesus monkeys with the OV40 virus was determined and frequent infection of monkeys of other species was also found when they were kept together with Macacus rhesus.

Twenty-six reports and talks were given over to the improvement of live poliomyelitis vaccine, and 24 reports on new data were presented and discussed on the nature of the viruses and their interrelations with the cells. The other reports were on problems such as the study of distinctive inhibitors of virus activity, formed in cultures of transplantable strains of cells free of viruses. These reports aroused great interest.

The Conference noted the great importance of theoretical studies presented in the field of genetics and physiology of viruses and experimental chemotherapy and recommended the further development of work along these lines, particularly on the study of the intracellular processes of virus multiplication and the biosynthesis of their components.

13. Levkovich, Ye. N. Seventh Joint Scientific Session of the Institute of Poliomyelitis and Virus Encephalitides of the Academy of Medical Sciences, USSR, and the Belorussian Institute of Epidemiology, Microbiology and Hygiene on tickborne encephalitis and other arbovirus diseases. IN: Academiya meditsinskikh nauk SSSR. Vestnik, no. 1, 1964, 89-90.

In 1963 the Seventh Joint Scientific Session of the Poliomyelitis and Viral Encephalitis Institute of Epidemiology, Microbiology, and Hygiene sponsored a discussion of the problem of tickborne encephalitis

and other arbovirus diseases which was held in Minsk. Representatives of scientific institutions of 28 cities in the USSR as well as scientists from Czechoslovakia, a total of 181 participants, took part in the Session. One hundred and twenty-four reports were given on problems of differentiation and classification of viruses of the tickborne encephalitis group, new methods of studying arbovirus diseases and problems of epidemic-control measures, as well as data on the distribution of other arboviruses on the territory of the Soviet Union.

Reports of the following Soviet scientis were presented: M. P. Chumakov, L. G. Karpovich, Ye. S. Sarmanova, G. I. Sergeyeva, M. V. Bychkova, V. O. Tapupere; and from Bratislava, Czechoslovakian scientists Ye. O. Libkova, V. Mayer, R. Rzegacek, O. Kozukh, and E. Eriek concerning the isolation of virus strains different from the viruses of the tickborne encephalitis isolated in Kemerovskaya oblast' from Izodes persulcatus ticks from sick persons with symptoms of an undetermined fevrile illness. It was determined that these strains are distinctly different from the viruses of the tickborne encephalitis group with respect to their behavior in tissue cultures, their range of pathogenicity for animals, and in their antigenic structure. The fact that the strains isolated were arboviruses was substantiated. On a comparative study of these strains with different serological groups of other arboviruses, the characteristics of the isolated virus, which the authors called the "Kemerovskiy virus," were demon-The finding of antibodies to this virus in the blood sera of human beings and animals in the region where the virus was isolated makes it possible to suppose that it has a possible role in human pathology and that it circulates in nature.

In reports of Ye. N. Levkovich, V. I. Votyakova, V. V. Pogodina, O. Ye. Rzhakhova, I. A. Robinzon, and others, the possibility was shown of isolating, as individual species, the viruses of Far Eastern and Central Europeam encephalitides, Scotish encephalitis, Povassan, Omsk hemorrhagic fever, Kyasanur forest disease, and the Malayan virus (Langat).

On problems of the selection of attenuated strains of tickborne encephalitis, a number of reports and communications were given by L. G. Stepanova, G. D. Zasukhina, V. I. Mayer, Ye. O. Libikova, P. I. Al'brekht, and M. K. Tyushnyakova. Data were presented on obtaining strains of the tickborne encephalitis virus with attenuated nervous system viru-A lively discussion revolved about the criteria characterizing attenuation of strains and possibiolities of utilizing the latter as a living vaccine. V. I. Il'yenko and A. A. Smorodintsev reported preliminary data on the testing of the immunogenic characteristics and side-effects produced by the live vaccine against tickborne encephalitis, prepared from the Malayan virus (Langat).

In the reports of V. I. Il'yenko, A. D. Al'tshteyn, N. V. Shalunova, A. G. Karpovich, Ye. N. Levkovich, and others, on the topic, "New Methods of Studying tickborne encephalitis," the studies dealt with the phenomenon of interference, the use of cultures and tissue, the hemagglutination-inhibition test, and others. It was shown that the interference phenomenon can be used for the demonstration in tissue culture of viruses which do not exert a cytopathogenic effect, for the titration of viruses, and for the determination of antibodies in blood sera. The accumulation of interferon in the tissue culture was noted.

A series of reports was given on the utilization of the cytopathogenic effect of the virus, immunofluorescence, the diffusion-in-gel test, plaque formation, and the hemagglutination-inhibition test by V. I. Votyakov, G. I. Sergeyeva, P. K. Al'brekht, Han Shih-Tse, P. S. Karaseva, N. V. Loginova, R. G. Desyatskaya, G. P. Pivanova, S. P. Karpov, L. A. Vereta, L. G. Karpovich, O. Ye. Rzhakhova, and others. Achievements in the field of applying tissue cultures to the study of tickborne encephalitis were presented. New serological methods, particularly the hemagglutination-inhibition test, have become extensively used in the practice of laboratory, clinical, and epidemiological research. The improvement of antigens for the hemagglutination-inhibition test as well as methods for eliminating nonspecific inhibition from them have been suggested.

A. A. Smorodintsev and S. A. A. Ananyan reported the use of the hemagglutination-inhibition test for the serological demonstration of arbovirus diseases, which made it possible to detect the existence of previously unknown foci of arthropod-borne diseases of group A, C, and Buniamwer (after Casals) in the territory of the USSR.

A comprehensive study was made of the mechanism of the circulation of the virus during the period of activity of ixodial ticks and outside of the period of the biocoenotic relationships of the tickborne encephalitis virus by zoologists, parasitologists, and virologists L. P. Nikiforov, Yu. A. Morozov, V. A. Bouko, L. A. Vereta, and others. work was accomplished in controlling tickborne encephalitis through the utilization of the characteristic features of landscape types of foci for epizootological and epidemiological prognoses. on the study of the natural foci of tickborne encephalitis in various geographic regions of the Soviet Union were obrained for Belorussia, the Ukraine, the Urals, Siberia, the Far East, Tatarskaya ASSR, Udmurtskaya ASSR, and others by V. I. Votyakov, L. V. Gromashevskiy, G. I. Netskiy, L. G. Tatarinova, G. Kh. Gil'manova, A. V. Mishin, V. I. Chabovskiy, and others.

The clinical aspect of the problem of tickborne encephalitis and the tendency toward tickborne encephalitis evolution as a clinical phenomenon was presented in a review report by A. G. Panov, as well as in reports of A. I. Shapoval, K. G. Umanskiy, R. M. Gurarly, and thers. The differentiation of Eastern and Western variants of tickborne encephalitis, reflecting the clinical characteristics and characteristics of the course of the disease, was considered sufficiently substantiated. It was recommended that the route of infection - arthropodborne or alimentary - be formulated in the diagnosis. Attention was called to the need for seeking out new, more effective methods and means of therapy.

In a report by D. K. L'vev and others, data on the extensive testing of cultured, inactivated vaccine against tickborne encephalitis were presented,

Epidemiological observations and serological experiments have shown that it produces no side effects and that it is highly effective immunologically.

APPENDIX III.

SOME SOVIET VIROLOGICAL RESEARCH INSTITUTES AND THEIR PERSONNEL

Introduction

The numerous Soviet institutions involved in virological research range from small stations or field hospitals dealing with specific problems to institutes covering the entire field. The latter perform the important research and publish most of the scientific materials on the subject. All-Union institutes also carry out studies directed toward policymaking and serve as advisory bodies to the Ministry of Health, USSR; the main virological institute in each Soviet Republic performs a similar function. Usually the central institute does research work and coordinates the studies of sanitation stations, public-health centers, and field hospitals. Among the leading institutes in Moscow are the D. I. Ivanovskiy Institute of Virology; Academy of Medical Sciences, USSR; the Institute of Policmyelitis and Viral Encephalitis, Academy of Medical Sciences, USSR; the Institute of Epidemiology and Microbiology, Ministry of Health, RSFSR; and the Scientific Research Institute of Viral Preparations. Institutes in Leningrad include the Institute of Experimental Medicine, Academy of Medical Sciences, USSR, and the Medical Institute of Sanitation-Hygiene; the Institute of Medicine and the Institute for the Advanced Training of Physicians are located in Kiev.

The following is a list of institutions which are engaged in virological or closely related research. Affiliated scientists are listed under each institution, along with any available information on their professional qualifications, positions, and honors conferred upon them.

APPENDIX TIT.

SOME SOVIET VIROT. OGICAL RESEARCH INSTITUTES AND THEIR PERSONNEL

All-Union Scientific Research Chemical-Pharmaceutical Institute im. C. K. Ordzhonikidze

Belikov, G. P. Daniyelyan, N. M.

Katunina, V. T. Pershin, C. N.

All-Union Scientific Research Institute of Railroad Hygiene, Ministry of Railroads, USSR

Ametirova, M. N.
Dubrovina, B. G.
Fayershteyn, S. G.
Kazakovtseva, Ve. D.
Koral'nik, B. P.

Kozina, T. P.
Kulinkova, N. K.
Parkhomenko, T. M.
Sokolova, N. N.

All-Union Scientific Research Institute of Veterinary Virology and Microbiology Ministry of Agriculture, USSR

"olosov, V. M. Nikitin, Ve. Ve. Pozdnvakov, A. A. Sargeyev, V. A. Syurin, V. N. Vladimirov, A. G.

Belorussian Scientific Research Institute of Epidemiology and Microbiology

Dir: Votyakov, Veniamin Tosifovich (specialty: virology). Doctor of Medical Sciences; Professor; Director of the Belorussian Scientific Research Thatitute of Epidemiology and Microbiology. Nominated for corresponding membership in the Academy of Medical Sciences, USSP by the academic councils of the Belorussian Institute of Foidemiology and Microbiology: the Belorussian Society of Epidemiologists, Microbiologists, and Infectious Disease Specialists; the Ministry of Health, Belorussian SSR, and the All-Union Scientific Medical Society of Epidemiologists, Microbiologists, and Infectious Disease Specialists im. I. I. Mechnikov.

Protas, T. T.

Central Asian Scientific Research Antiplague Institute, Alma-Ata

Shashayev, M. A.

Central Institute for Advanced Training of Physicians of the Academy of Medical Sciences, MSSR

Pir: M. D. Kovrigina

Bektimirov, m. A. cutikina, A. V. Matyukova, Yu. N. Sumarokov, A. A.

Sarayeva, N. Т. Sokkar, T. M. Varoslavskaya, N. V.

Central Scientific Research Institute of Epidemiology, Ministry of Health, USSR

Pille, E. R.

Control Institute for Medical and Piological Preparations im. L. A. Tarasevich.

Al'tshteyn, A. D. Kravchenko, A. T.

Donetsk Province Sanitary Epidemiological Station Anishchenko, G. A.

Corki Scientific Research Institute of Epidemiology and ™icrobiology

Dir. I. N. Blokhina

Nogicheva, M. A.

Institute for Advanced Training of Physicians. Kiev. Zhalko-Titarenko, V. P.

Institute of Foldemiology and Microbiology. Kiev.

Dyadichev, N. R.

Institute of Epidemiology and Microbiology im. N. F. Camalei of the Academy of Medical Sciences, USSR

Al'tshteyn, A. D. Ket Avakyan, A. A. Kin Fedorov, Yu. B. May Kats, L. N. Min Kaulen, D. P. Pay

Ketiladze, Ye. S. Kirillova, F. M. Mayorova, G. G. Mirolyubova, L. V. Pavlova, I. B.

Solov'yev, Valientin Dmitriyevich (specialty: virology). Corresponding Member of the Academy of Medical Sciences, USSR; Doctor of Medical Sciences; Professor; State Prize Winner; Head of the Section of Virology, Institute of Epidemiology and Microbiology im. N. F. Gamaley of the Academy of Medical Sciences, USSR; Head of the Chair of Virology, Central Institute for Advanced Training of Physicians. Nominated for active membership in the Academy of Medical Sciences, USSR, by the academic councils of the Institute of Epidemiology im. N. F. Gamaley of the Academy of Medical Sciences, USSR, Central Institute for Advanced Training of Physicians of the Academy of Medical Sciences, USSR, Institute of Poliomyelitis and Viral Encephalitis of the Academy of Medical Sciences, USSR, Institute of Virology im. D. I. Ivanovskiy of the Academy of Medical Sciences, USSR, and the Board of the All-Russian Society of Epidemiologists, Microbiologists, and Infectious Disease Specialists.

Institute of Experimental and Clinical Oncology, Academy of Medical Sciences, USSR

Dir: A. I. Serebnov

Mazurenko, Nikolay Petrovich (specialty: virology)
Doctor of Medical Sciences; Head of the Laboratory
for Pathology of Leukoses, Institute of Experimental
and Clinical Oncology of the Academy of Medical
Sciences, USSR. Nominated for corresponding membership in the Academy of Medical Sciences, USSR,
by the academic councils of the Institute of Exper-

imental and Clinical Oncology of the Academy of Medical Sciences, USSR and the Board of the All-Union Scientific Medical Society of Epidemiologists, Microbiologists, and Infectious Disease Specialists im. I. I. Mechnikov.

Institute of Medical Parasitology and Tropical Medicine, Ministry of Health, USSR

Naumov, R. L.

Pospelova-Shtorm, H. V.

Institute of Medical Radiology of the Academy of Medical Sciences, USSR

Dir: G. A. Zedgenidze

Cherkasov, V. F. - Manager of Scientific Methods Department Chermyakhovskaya, A. K. Filatov, P. P. Yelashov, Yu. G.

Institute of Zoology and Parasitology, Academy of Sciences, Uzbek SSR

Lakhanov, Zh. L.

Institute of Poliomyelitis and Viral Encephalitis of the Academy of Medical Sciences, USSR

Dir: Chumakov, M. P.

Agol, V. I.
Al'tshteyn, A. D.
Avakyan, A. A.
Bannova, G. G.
Bychkova, M. V.
Gnuni, I. M.
Gagarina, A. V.
Gavrilovskaya, I. N.
Gol'dfarb, L. G.
Iyks, S. R.
Kalinina, L. I.

Karmysheva, V. Ya. Karmysheva, V. Ya. Karmysheva, L. G. Khanina, M. K. Khan Shi-tsze Levina, L. S. Levkovich, Ye. N. L'vov, D. K. Malygina, I. G. Pistsov, N. G. Pogodina, V. V. Rodin, I. M.

Sarmanova, Ye. S. Selimov, H. A. Sergeyev, N. N. Shalunova, H. V. Shirman, G. D.

Shoshiyev, L. N. Svet-Moldavskaya, I. A. Svet-Moldavskiy, G. Ya. Tsilinskiy, Ya. Ya. Vil'ner, L. M.

Volorshirova, Marina Konstantinovna (specialty: virology) Doctor of Medical Sciences; Professor; Head of the Section of Poliomyelities and Entervoviral Infections, Institute of Poliomyelitis and Viral Encephalitis of the Academy of Medical Sciences, USSR. Nominated for corresponding membership in the Academy of Medical Sciences, USSR, by the Council of the Institute of Poliomyelities and Viral Encephalitis of the Academy of Medical Sciences, USSR.

Yan Zhu su Zaklinskaya, V. A.

Institute of Virology, Czechoslovak Academy of Sciences. Bratislava.

Albrecht, P. Blaskovic, D Brauner, I. Jakubik, J. Jasinska, St. Lesso, J.

Link, F. Mayer, V. Rada, B. Sadecky, E. Skoda, R.

Institute of Virology im. D. I. Ivanovskiy of the Academy of Medical Sciences, USSR

Dir: V. M. Zhdanov - Corresponding Member of the Academy of Medical Sciences, USSR

Bekleshova, A. Yu. Beletskiy, V. D. Berezina, O. N. Bukrinskaya, A. G. Burducheva, O. Buzinov, I. A. Bychkova, Ye. N. Chervonskiy, V. I. Danilov, A. I. Dmitriyeva, R. A. Dormidontov, R. V. Dreyzin, R. S. Feklisova, L. V.

Gaydamovich, S. Ya. Gitel'man, A. K. Gorshunova, L. P. Gromykov, A. I. Kantorovich, R. A. Kareva, M. P. Kaverin, N. V. Ketiladze, Ye. S. Klimenko, S. M. Klisenko, G. A. Konovalov, G. V. Kosyakov, P. N. Kozlova, I. A.

Kozlyakova, A. I.
Kurbanov, I. A.
Li Yuy
Lipmind, H. A.
Markaryan, A. G.
Medvedeva, G. I.
Mekler, L. B.
Mel'nikova, L. A.
Horoz, A. G.
Naumova, V. K.
Obukhovskaya, N. M.

Parfanovich, M. I. Peterson, O. P. Popova, O. M. Posevaya, T. A. Priymyagi, L. S. Razulakhova, E. B. Rovnova, Z. I. Ryutova, V. P. Sergeyenko, A. D. Shen, R. M.

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